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## ELECTRONIC THEORIES

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*Received June 24, 1936*

Unless we are willing to take the view of Bishop Berkeley that we know nothing which occurs outside of our own bodies and that our senses and the testimony of others are untrustworthy, we must consider that it is the function of science to acquire the best knowledge possible about everything with which our intellectual lives are concerned. In this category I include feeling and will of the old philosophy and not merely physics and biology. Hypotheses and theories are not merely temporary tools for the direction of our experimental work, but are the necessary method by which we gain a better insight into the character of a real, intelligible, and dependable universe, which is logically interrelated in all its parts.

In discussing electronic theories, therefore, I wish to pick out, so far as I can, the origin of those ideas which still guide us in the development of the subject. As with all other branches of science, the first ideas were based on simple observations and were crude and partly erroneous. The grave danger, today, is that a scientist who is working in some narrow part of this field, such as the beautiful and accurate conclusions from wave quantum mechanics, x-ray analysis, thermodynamics, or statistical mechanics, is liable to disregard results obtained in the older fields of valence, structure of organic compounds, optical activity, and molecular volumes. Each of these must be carefully checked by the others before we can hope for a true picture of the whole field.

I cannot refrain from stopping for a moment to remark the same danger in economics and in international relations. Manufacturers and bankers who think that they can base their operations solely on the motive of profit and disregard the motive of service, and statesmen who think they can consider exclusively the interests of their own nation and disregard the interests of other nations, are likely to be brought up with a jolt, as manufacturers have been in our six years of depression, not yet over, and as the world was in the Great War.

Some of the ideas on which our electronic theories rest go back more than

<sup>1</sup> Priestley Medalist, Ninetieth Meeting of the American Chemical Society, held at San Francisco, August 19-23, 1935.

two hundred and fifty years, and some hypotheses which seemed at that time wholly incompatible have been reconciled in the twentieth century. Such a result is not infrequent in physics and chemistry.

In what follows an attempt is made to state the origin of the ideas which seem most important and to tie them together into a logical, comprehensive system, pointing out where earlier ideas have been imperfect or confusing.

### LIGHT

1680-1700. Near the close of the seventeenth century Newton proposed his "corpuscular" (atomic) theory of light, and Huyghens proposed the undulatory theory. It was not until the twentieth century that it was demonstrated that each theory is partly right.

1818. Fresnel showed that a beam of monochromatic light, separated into two parts which are brought together after travelling paths of different lengths, give alternate light and dark bands. He concluded that light is an undulatory motion in a hypothetical medium called the ether.

1814. Fraunhofer discovered and mapped many of the dark lines of the solar spectrum without understanding their significance.

1860. Bunsen and Kirchhoff showed that the light emitted by sodium in a Bunsen flame or by iron in an electric spark has the same frequency (wave length) as the light absorbed by these elements in the gaseous state. This gave a satisfactory explanation of the Fraunhofer lines and has revealed the composition of the sun and stars and demonstrated the unity of the universe.

More than half a century later, Planck, Bohr, and others developed the theory that light consists of photons having characteristic frequencies, and that a photon of the right frequency may impart its energy to an electron in the shell of an atom and cause it to rise to an orbit further from the nucleus; also that the electron will, later, fall back to its original orbit, emitting a photon of the same frequency as that of the photon taken up or two or more photons of a smaller frequency.

The long waves of Hertz used in wireless telegraphy, the x-rays of Röntgen, the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -rays of Becquerel, the Curies, and Rutherford, and the "cosmic" rays of Kuhlörster, Millikan, and Compton need only to be mentioned here.

In an important sense photons may be thought of as the connecting link between matter and energy.

### ELECTRICITY

1729. Gray showed that metals (elements whose valence electrons are loosely held, allowing them to pass easily from one atom to another through a wire) conduct electricity, while glass, sulfur, and resins do not.

1735. Dufay distinguished between vitreous electricity, obtained by rubbing glass, and resinous electricity, obtained by rubbing amber and other resinous substances, and found that bodies charged with electricity of the same kind repel each other, but that if charged with different kinds they attract each other. This is the most fundamental postulate in all electronic theories, but the question of how bodies not in contact can attract or repel each other has not been solved.

1747. Franklin, in a letter to Peter Collison in England, suggested his "one fluid" theory, calling bodies which contain an excess of the "fluid" positive and those with a deficiency negative. He was dealing with electrons in his experiments and his theory was fully justified, but through a mistake in interpreting his experiments he called bodies charged with resinous electricity (containing an excess of electrons) negative.

In 1786 Galvani discovered current electricity, and about 1800 Volta invented the first primary batteries.

1790. Lavoisier came to think of oxygen as the central element of chemistry and defined acids as the oxides of non-metals, bases as oxides of metals, and salts as compounds of acids and bases.

Davy, making use of a battery devised by Volta, prepared metallic potassium; in 1807 he proposed (9) an electrochemical theory in which oxygen was positive toward non-metals and negative toward metals. Berzelius (4) developed this into the old electrochemical theory, which dominated chemistry for thirty to fifty years. In salts the base was



positive and the acid negative;  $\text{CaO} \cdot \text{SO}_3$ . After this theory fell into disrepute for the last half of the nineteenth century, new electrochemical theories retaining some of the ideas of the older theory were proposed by Arrhenius, Abegg, Lewis, and Kossel.

1831. Faraday demonstrated the interconvertibility of electrical and mechanical energy and formed very clear ideas about electrical fields and magnetic lines of force. Maxwell (43) in his *Electricity and Magnetism*, published in 1873, translated Faraday's ideas into accurate mathematical language and laid the basis for the methods used by electrical engineers ever since. His object was "to construct a theory of electricity in which action at a distance should have no place." He succeeded by means of the theory of an ether. Weber and Kohlrausch had previously demonstrated the remarkable fact that the ratio of the electromagnetic and electrostatic units of electricity is the velocity of light. This fact and the studies of Maxwell gave the electromagnetic theory of light; from that time on it has been necessary to consider light and electricity as two phases of the same subject. To these we must now add atomic phenomena, so that mechanical energy, light, electricity, and chemical atoms are inseparably connected with each other.



## ATOMS

1807. Dalton first gave to the theory that material substances are composed of minute, individual particles, a form which connected it with their quantitative composition and made it practically useful. The theory was known to the ancients as a philosophical speculation, but no one had been able to connect it accurately with experimental observations.

Dalton's crude and partly erroneous system, which for many years left many chemists in doubt whether true atomic weights could ever be determined, was developed by steps so well known that they need only to be mentioned—Avogadro's law, the law of Dulong and Petit, the isomorphism of Mitscherlich, and the Periodic System of Newlands, Mendeléef, and Lothar Meyer. The visit of Cannizzaro to Karlsruhe in 1858, where he made such a convincing presentation of the law of Avogadro that the adherence of German chemists was secured, must be recognized as one of the factors in the rapid advances which followed.

The democratic methods of research developed in Liebig's laboratory, the "type" theory of Gerhardt and Laurent, and Frankland's theory of valance had already laid the foundation for a rapid development of organic chemistry. Cannizzaro's visit came the same year that Couper and Kekulé proposed, independently, the theory of chains of carbon atoms, and for the thirty years that followed hundreds of students flocked to Germany to study chemistry. Pasteur had already discovered the optical dissymmetry of tartaric acid and had prepared the way for the thought of Le Bel and van't Hoff that the four groups attached to a carbon atom are more or less held in a somewhat rigid, irregular dissymmetry about it. This led, further, to the thought of Wislicenus that doubly united carbon atoms and rings give a *cis* and *trans* isomerism. The return of foreign chemists from Germany to their homes, where they established new centers of research, and the publication in German journals of articles from other countries, and especially from America, gave an era of international coöperation in science never before equalled.

Unfortunately, since the World War, an era of supernationalism, so dangerous for international relations and so disastrous for the world's economic progress, finds its counterpart in science. Each nation thinks that it must develop its own scientific literature as independently as possible; Holland, Germany, and France follow Kossel's theory of intramolecular ions, while American and English chemists follow G. N. Lewis' idea of shared electrons, and many of them are doubtful about intramolecular ions.

Kossel and Lewis proposed their theories quite independently in 1916, but the theories rest on a common background and some of their details are identical. Soon after, the two men were on opposite sides in the great conflict. When we remember the confused and conflicting systems of

atomic weights during the first half of the nineteenth century and how these were reconciled in a single system which has not been questioned for seventy-five years, we may feel sure that our electronic theories will be fused into a consistent, comprehensive whole. May we not take that as an omen—that Eden and Hitler, who were in trenches opposite each other across the battle line, may help to build that permanent peace which we all so earnestly desire? All sensible men now see that war in the twentieth century is a senseless and useless anachronism and, in spite of the reactionary tendencies of Japan and Italy, I have the faith to believe that the statesmen of the world will consolidate a peace in which all nations must be considered as equals. The unification of electronic theories is the work of hundreds of individuals. The new world order growing before our eyes is the work of thousands, and we as scientific men must see our obligation to “do our part” in this great coöperative and democratic undertaking.

1834. Faraday (13) discovered the fact that if the same electric current is passed through a series of solutions of electrolytes, the quantities of the elements liberated at the electrodes in each solution are proportional to the atomic weights of the elements. It should be remembered that at that time physicists and chemists were not very confident that the accepted atomic weights were really proportional to the weights of the actual atoms. Faraday drew no theoretical conclusions.

Helmholtz (22) drew, for the first time, the logical conclusion that there are two equal and opposite atoms of electricity. Such an idea was quite foreign to the thought of the chemists and physicists of that time. The negative electron was not discovered until 1897 and the positron in 1933.

1878. Crookes (8) had discovered the cathode rays, which are a stream of electrons, shortly before, and had demonstrated that they have mass and an electrical charge.

J. J. Thomson (92) and Kaufmann (25) discovered the electron in 1897.

Michelson and Morley (45; see also 46), in 1886–87, demonstrated that the velocity of light is independent of the direction in which the earth is moving. This is inconsistent with the theory of an all-pervading ether as the medium for the transmission of light, and was one of the reasons which led Einstein to propose his theory of relativity (10).

1901. Planck (74) proposed the theory that radiant energy is emitted, transmitted, and taken up only in definite units which he called quanta. This theory was later developed by Planck, Einstein (12), and others.

Planck's quanta may now be defined as atoms of radiant energy and are identical with photons and with Newton's corpuscles of light. They are of an infinite variety, each having a definite frequency,  $\nu$ , found by dividing the velocity of light,  $3 \times 10^{10}$  cm. per second, by the wave length of the photon, and a definite energy,  $h\nu$ , in which  $h$  is Planck's constant,  $6.5 \times 10^{-27}$  erg seconds.

Einstein (11) in 1905 also made the statement, "The mass of a body is a measure of its energy content. If this energy changes by  $L$ , the mass changes by  $L/9 \times 10^{20}$ , the energy being measured in ergs and the mass in grams." The denominator of the fraction,  $9 \times 10^{20}$ , is the square of the velocity of light.

This ratio between mass and energy may also be stated by saying that one gram is equal to one erg multiplied by the square of the velocity of light.

These theories, together with the discovery of radium by the Curies, the disintegration of atoms by Rutherford, the transmutations of atoms by many chemists and physicists, of isotopes by McCoy, Boltwood, Thomson, and Aston, of the interferences of protons and electrons similar to the interferences of waves of light, the demonstration by Rutherford (77) that an atom consists of a small nucleus with a multiple positive charge, surrounded by electrons, and the discovery of the positron by Anderson (3) have given in the twentieth century quite new concepts about the universe in which we live. The only ultimate entities about which we can speak with some assurance are protons or neutrons, electrons, positrons, and photons. This recalls how Ostwald at St. Louis in 1904, after his genial remarks about a lecture by van't Hoff on atoms, picked up a piece of chalk and wrote under "Radioactivity," "explodirt," and under the whole, "Energie."

G. N. Lewis (40), when he was teaching a class in elementary chemistry in 1902, seems to have made the first attempt to connect electrons with chemical phenomena by means of his first crude sketches of the "cubical" atom. He thought his attempt too speculative, however, and it was not until fourteen years later that he published his theory.

J. J. Thomson (93) in 1904 gave the first published electronic theory of chemical combination. He supposed that an atom consists of a uniform sphere of positive electrification and that electrons within such a sphere arrange themselves according to their attraction toward the center and their repulsion from each other. This proposal was accompanied by a careful mathematical analysis. The incident illustrates the uselessness of mathematics when the postulates employed are wrong.

The fundamental idea of the static attraction between atoms when an electron is transferred from one atom to another is still valid, however, for isolated atomic ions, but the use of the hypothesis to explain homoöpolare unions, by Falk and Nelson, Fry, Noyes, and others, delayed the acceptance of the theory of G. N. Lewis.

1904. Abegg (1) proposed his system of "principal" and "contra" valences, e.g., for chlorine, one principal (negative) valence toward hydrogen and seven contra (positive) valences toward oxygen. This has some

resemblance to the old electrochemistry and evidently had a great influence on Kossel and Lewis in the development of the theories which they proposed in 1916. At the close of his paper Abegg proposed an electronic interpretation.

1911. Rutherford (77), by a study of the scattering of alpha particles shot through a thin film of gold, demonstrated that the positive nucleus is small and is surrounded by electrons. This has been accepted as the basis for all subsequent theories of the electronic structure of atoms.

1913. Bohr (5) proposed his theory of atoms as consisting of positive nuclei surrounded by rotating electrons arranged in groups at successive energy levels. In the heavier atoms these groups contain, when complete, 2, 8, 18, and 32 electrons. Each noble gas contains in its outer group 8 electrons, and the next atom in the Periodic System begins a new group with a single electron. By combining this with the quantum theory of Planck and Einstein, which is now interpreted by means of photons, Bohr was able to give an explanation for the Rydberg, Balmer, Lyman, and other series of spectral lines.

In some of its details Bohr's theory has not been entirely satisfactory and it has been replaced by, or, speaking more accurately, it has been developed into the wave quantum mechanics. It still remains the only satisfactory mechanical picture that we have for the relation between the electrons and nuclei of atoms and molecules. It is of especial value because it emphasizes the fact, which no one questions, that each electron retains its identity and does not merge with other electrons in any ordinary chemical process.

1915. Parson (71) published a paper entitled, "A Magneton Theory of the Structure of the Atom." Owing to the medium of publication, which was occasioned by the difficulty of securing the publication of a long theoretical paper, Parson's paper has not received the attention which it deserves. Lewis refers to it several times in his book on valence and acknowledges his indebtedness to Parson for some of the ideas which he used.

1916. Kossel (30) proposed an electronic theory of the structure of atoms and molecules based on Abegg's principal and contra valences and Bohr's theory of atomic structures. This was proposed in Germany at the same time that Lewis' theory was proposed in America. The two theories were developed independently but have a common background, causing them to have a number of identical ideas. Indeed, many chemists seem to think that there is little difference between the two theories.

The most significant principles in Kossel's theory are as follows:

1. All elements after helium have an inner group of electrons, called by Lewis the *kernel*, which has the structure of the next preceding noble gas.

2. The electrons which take part in ordinary chemical reactions are situated outside the kernel. It is now recognized that in the longer periods there are two energy levels outside of the kernel for some of the atoms and that in some atoms electrons may be transferred from one of these levels to the other, e.g., for iron.

3. Electrons may be transferred from one atom to another, the atom losing an electron becoming positive and the one receiving it becoming negative.

4. Elements just above a noble gas lose electrons easily; those just below gain them easily.

5. Elements of the first two periods may lose all their valence electrons. Chlorine may become heptapositive and sulfur hexapositive. This is a very important difference from Lewis' theory and a most objectionable feature.

6. Atoms are held in combination as intramolecular ions. Carbon is negative in methane and positive in carbon tetrachloride.

7. No definite location for the valences of atoms is attempted. The theory furnishes no explanation for optical dissymmetry or *cis-trans* isomerism. Some of the later developments of Lewis' theory do this.

8. In papers published in 1919 and 1920, Kossel (31) discusses homo-polar compounds at some length and presents some ideas which approach those of Lewis closely.

Georg Hahn (19) has recently made an attempt to account for homo-polar unions on the basis of Lewis' theory but has shown little understanding of the way in which the theory has been developed in America and in England.

1916. G. N. Lewis (39) published in the same year as Kossel an electronic theory of the structure of atoms and molecules, which he had been considering for fourteen years and had often discussed with his colleagues at the University of California. This theory now receives almost as general acceptance in America and England as the theories of structural organic chemistry. Lewis acknowledges his indebtedness to organic chemistry and to his discussions with Parson while formulating the theory. It has been developed and modified by hundreds of chemists, physicists, and astronomers (65, 67). Not all of these have given proper consideration to the work of others and not all have remembered facts and ideas which have come down from pre-electronic times.

The brilliant presentation of Lewis' theory by Langmuir (34) contributed very much to its rapid acceptance in America. Langmuir suggested the term "covalence," which has become very useful. He also discussed the relation between isosterism and isomorphism and electronic structures.

The following ideas in Lewis' theory and in its development by others seem most important:

1. Electrons, both in atoms and in molecules, usually occur in pairs. Odd electrons are magnetic (14, 33, 73, 90, 91). Because of their "spins" (18) in opposite directions (54), pairs of electrons are non-magnetic.

2. Helium has a pair of electrons. This pair is repeated in all atoms except hydrogen, and the x-ray spectra of these electrons (K series, Moseley (47)) furnishes the best basis for determining the position of an element in the Periodic System and for identifying a new element.

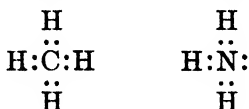
3. All other atoms have a "kernel" with a structure the same as that of the next preceding noble gas, or, for atoms having two energy levels for electrons outside of that structure, a secondary, intermediate kernel.

4. Atoms have a tendency to assume the electronic structure of a noble gas or of the intermediate kernel. They may do this in two ways.

5. *Atomic, ionic valences.* By losing the valence electrons exterior to either of the kernels defined in paragraph 3, or by taking up electrons and assuming the structure of the kernel of the atoms of the next period. Ions of these types are identical with the ions of Kossel's theory, e.g.,  $\text{Na}^+$  and



6. *Covalences.* By sharing pairs of electrons, e.g.



It is here that Lewis's theory differs radically from that of Kossel, who in his first paper thought the carbon of methane negative. There has been a closer approach to Lewis in the later papers quoted and especially in some of the later expositions of his theory. With the exception of a very few compounds of nitrogen, the elements between boron and scandium all have a valence shell of four, five, or six pairs of electrons. Some chemists have assumed "singlet" bonds formed by single electrons, but well-established bonds of this type are rare. Compounds with four pairs of electrons in the valence shell are by far the most common. Some pairs are unshared, as in ammonia, nitric acid, and many other compounds.

In his first paper Lewis thought of the pair of electrons as in a static position between the two atoms. In his book (pp. 56, 57) he inclined to ascribe orbital motions to the electrons. In the paper last quoted (39) he accepted a tetrahedral arrangement for the orbits of the four pairs of electrons. A similar conclusion has been reached by Pauling (72) and by Slater (84) on the basis of quantum mechanics.

7. *Inclusive orbits.* In 1917 the author (50; see also 15) suggested that two atoms might be held together by an electron which included two positive nuclei in its orbit. The suggestion was erroneous in several particulars and has had no effect in the development of our theory. In 1923, N. R. Campbell (6), Sidgwick (79), and C. A. Knorr (27) made a similar suggestion for pairs of electrons. The close relation between these suggestions and quantum mechanics is evident. Dynamic relations between electrons and nuclei are certainly much more acceptable than static ones.

8. *Relation of the electron pair to the atoms held together.* The original idea of Lewis that the pair are situated between the atoms has led some chemists to speak of them as closer to one of them than to the other. In a certain sense this is true. The nitrogen atom of nitrogen trichloride will usually retain the covalent electrons when a chlorine atom separates from it, while the phosphorus atom of phosphorus trichloride will allow a chlorine atom to carry away the pair of electrons, because nitrogen has only two electrons in its kernel while phosphorus has ten (55). Stieglitz expresses this relation by a plus and a minus sign between the two atoms, placing the plus sign next the atom which remains positive.

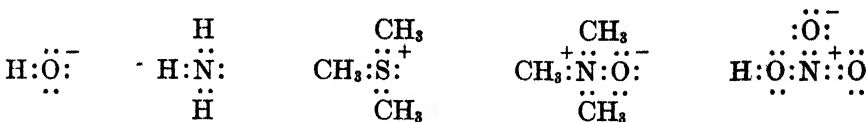
While it is clear that in the sense just stated the electron pair is not equally shared by the two atoms, it should always be remembered that, so far as atoms at a distance are concerned, the pair balances a unit positive charge in each of the atoms. In current literature authors frequently speak of positive charges as shifting from one atom to another. This is impossible; because the positive charges of every system are fixed and indivisible and are located in the nuclei of the respective atoms of the system. Any apparent shift of a positive charge must be due to a shift of the electrons in accordance with the rule given in paragraph 9 for complex and intramolecular ions.

The "polar environment" of which Lewis (37), Ingold (23), Kharasch (26), and many others speak, whether intramolecular, as in induced polarity, or extramolecular, as in the solvent, may have a large effect on ionization (e.g., chloroacetic acid) or on the course of reactions.

External, unshared electrons may also give a dipole moment to molecules and a negative effect in relation to nearby atoms, but that a single covalence can give rise to electromers does not seem consistent with the idea of inclusive orbits. See, however, Stieglitz (86), who holds a different view.

9. *Complex ions. Intramolecular ions.* In every electrically neutral molecule which is not a complex ion and which does not contain an intramolecular ion, the sum of the covalences and unshared electrons is equal to the kernel charge for each atom. Conversely, any atom in a compound for which the sum of the covalences and unshared electrons is greater or

less than its kernel charge is either an intramolecular ion or the significant part of an intramolecular or intermolecular ion; e.g.,



In trimethylammonium oxide, the oxygen atom with a single covalence is a negative ion and the trimethylammonium group is a positive ion. The latter is demonstrated by the fact that if the oxide is treated with hydrobromic acid a hydrogen atom is added to the oxygen ion making that electrically neutral, and the positive trimethylhydroxyammonium ion formed has a high conductivity characteristic of quaternary ammonium ions (52). The fact that one of the oxygen atoms of nitric acid is semi-ionic is demonstrated by the parachor of the nitric esters and nitro compounds. These two cases demonstrate that a nitrogen atom with four covalences is always positive, irrespective of the atoms with which it is united. It also confirms the principle implied in the rule that while the covalence pair is not equally shared when the atoms are different, the inequality of sharing is not so great as to cause one of the atoms to become an ion with respect to the other.

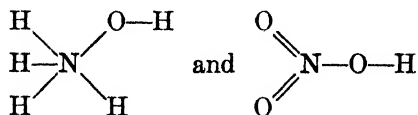
Some of my friends have objected to the term "ion" as applied to atoms and groups which do not move in reference to their companions. The word is constantly used for similar relations in the expositions of Kossel's theory and I know of no satisfactory substitute. The word "ion" has three important meanings designated by the single word: (1) An atom or group with a positive or negative charge. (2) Such an atom or group which is balanced by another atom or group having a charge of the opposite sign in the neighborhood. (3) An atom or group which moves independently through a solution under the influence of a potential gradient. The ions under discussion have the first two characteristics, but not the third. The sodium and chlorine atoms of crystallized sodium chloride do not have the third characteristic, but I think no one would hesitate to call them ions. We do not hesitate to call the atomic weight of chlorine 35.458, although we know that no single atom of chlorine has this atomic weight.

The rules given at the beginning of this section were published eight years ago (56), and no one has been able to cite a reasonable electronic structure for a compound which does not agree with the rule. The rules make it clear that the character of a complex ion or an intramolecular ion is just as definitely fixed by the relation between the kernel charge and the valence shell of some atom in the group as an atomic ion is characterized by the relation between its kernel charge and the next noble gas above or



below it in the Periodic System. The rules are especially useful for the light they throw on the nature of Werner's coordinated compounds. They also emphasize the fact that positive charges are indivisible and change only by whole numbers. They shift from one atom to another by shifts of electrons in the valence shells of covalent compounds.

Thirty years ago the structural formulas in common use for ammonium hydroxide and nitric acid were,



The nitrogen was quinquevalent in both formulas, and it was not altogether clear why one compound should be a very weak base and the other a very strong acid.

In 1912 an attempt (49) was made to explain this phenomenon on the basis of Thomson's theory that atoms are held in combination by static attraction due to the transfer of an electron from one atom to the other:

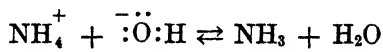


It seemed evident that the negative nitrogen of the ammonium hydroxide would hold the hydroxide ion less firmly than the positive nitrogen of the nitric acid.

The electronic formulas now used give a much better explanation:



The nitrogen is quinquevalent in both formulas, and each nitrogen atom has four covalences and one ionic valence, but with the difference that the ionic valence of the nitric acid is of the semi-ionic type (see below). In addition to this the ionization potentials of the ammonium group and of water must be nearly equal, with the result that because of the equilibrium,

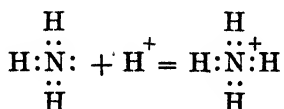


there can be very few of both ammonium and hydroxide ions present in the same solution. No similar relation exists for the nitric acid.

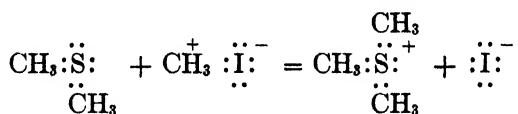
Ammonium hydroxide, so far as it exists in the solution, is probably a base of about the same strength as potassium hydroxide. A solution of ammonia in water is a weak base because very few molecules of ammonium hydroxide are present.

It is worth while to remark that the ammonium ion has almost the same electronic structure as the potassium ion and the two ions closely resemble each other, as methane and argon resemble each other (15, 50).

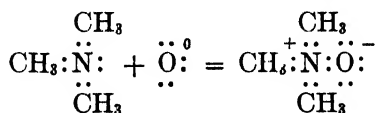
10. "*Donor*" and "*acceptor*." In discussing coördination, Sidgwick (83) calls an atom which furnishes both of the electrons to form a covalence a "*donor*" and the atom which receives the electrons an "*acceptor*." These terms have a much wider application than Sidgwick seems to have recognized and are very useful. Three simple illustrations are the following: The addition of a hydrogen ion to ammonia



The addition of a positive methyl ion to dimethyl sulfide,



The addition of an oxygen atom from ozone to trimethylamine,



Sidgwick recognized that a donor which exchanges a pair of unshared electrons for a covalence becomes more positive and the acceptor becomes more negative. The discussion of the nature of covalences and the illustrations prepare us for the following useful rules: In forming a covalence the donor increases its positive charge by one unit; the acceptor decreases its positive charge by one unit (64).

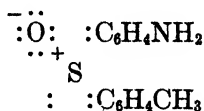
11. *Semi-ionic bonds*. Lowry (42) seems to have been the first to recognize clearly that double bonds may be of two types,—double covalences and half covalence and half ionic valence. Lowry called the latter mixed double bonds. Sugden (88) called them semipolar bonds. The term semi-ionic seems to be more suitable, because some compounds which are not semi-ionic show polarity because of unshared electrons.

In discussing the electronic structure of the perchlorate, sulfate, and orthophosphate ions, Lewis (38) says, "We may now write formulae in which an atom of oxygen is tied by only one pair of electrons to another atom and yet have every element in the compound completely saturated." Such a statement seems to imply that the oxygen atom which had been considered bivalent becomes univalent in these compounds. The semi-ionic formulas show at once that the oxygen is still bivalent in these ions and also show why the perchlorate ion is unibasic and the sulfate ion bibasic.



Chlorine has a kernel charge of seven. Four of these are balanced by the covalences with the four oxygen atoms, and the other three by three negative ionic valences of oxygen atoms, leaving one negative valence for the perchlorate ion. Sulfur has a kernel charge of six. Four of these are balanced by the four covalences of the oxygen atoms and two by the negative ionic valences of oxygen atoms, leaving two negative valences for the sulfate ion.

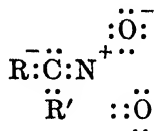
12. *Double and triple covalences.* Kopp (29), by determining the molecular volumes of compounds at their boiling points, discovered that an oxygen atom fills a greater volume when it is "in a radical" (i.e., when it has a double covalence) than it fills when it is "outside the radical" (i.e., has two single covalences). Sugden (87) has developed a function called the parachor, which depends on the properties of compounds at their critical temperatures. This has shown, more accurately, the same differences between single and double covalences that had been found by Kopp, and has shown that the parachor is still further increased by a triple covalence. The parachor of an oxygen atom with a semi-ionic union indicates a single covalence (89). This has been particularly interesting and valuable for the sulfinic compound (21),



If there were a double covalence between the oxygen and sulfur, the compound would be optically inactive. The parachor has demonstrated a semi-ionic union with a single covalence. This also confirms the evidence from active sulfonium compounds



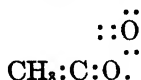
and from the active sodium salts of aliphatic nitro compounds studied by Kuhn (32) and Shriner (78),



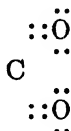
that a pair of unshared electrons may furnish the fourth element in tetrahedral dissymmetry.

The greater volume occupied by atoms held together by a double covalence, in spite of the fact that other methods have shown that the centers of the atoms are closer together than when they are held by a single covalence, seems to indicate that the tendency to a tetrahedral arrangement causes the pair of electrons to extend out on both sides of the line between the atoms. This is consistent with the *cis-trans* isomerism characteristic of such compounds and recalls Baeyer's Strain Theory. He thought the double union the limiting case of rings.

13. *Free radicals; odd electrons.* Kolbe (28) discovered that the electrolysis of potassium acetate gives ethane and carbon dioxide. The removal of an electron from the acetate ion gives the ephemeral compound,

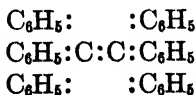


with an odd electron on the oxygen atom. The oxygen captures an electron from the covalence between the methyl and the carbon, and carbon dioxide is formed by rearrangement.

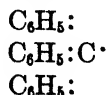


The methyl with an odd electron unites with another to form ethane,  $\text{H}_3\text{C} : \text{CH}_3$ . A very reactive free methyl radical was postulated to explain the course of the reaction long before an electronic interpretation was possible.

Gomberg (17) in 1900 discovered hexaphenylethane,

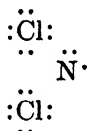


which he called at first triphenylmethyl,

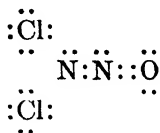


because hexaphenylethane dissociates readily to this "free radical," which reacts with iodine to give triphenylmethyl iodide and with oxygen to give triphenylmethyl peroxide. Later, other workers isolated other similar free radicals which were sufficiently stable to exist as independent molecules. These were the first free radicals of this type to be isolated as independent molecules. More recently, Paneth (70) and Rice (75, 76) have demonstrated the existence of ethyl and methyl as free radicals for a very brief but measurable time.

At  $-80^\circ\text{C}$ ., nitric oxide,  $\ddot{\text{O}}::\ddot{\text{N}}\cdot$ , which has a free electron, takes a chlorine atom with a free electron,  $:\ddot{\text{Cl}}\cdot$ , from nitrogen trichloride forming nitrosyl chloride,  $\ddot{\text{O}}::\ddot{\text{N}}::\ddot{\text{Cl}}:$ , and leaving nitrogen dichloride.



The latter unites with a second molecule of nitric oxide to form dichlorodinitrogen oxide



This immediately decomposes at  $-80^\circ\text{C}$ . into free chlorine and nitrous oxide,  $:\text{N}::\overset{+}{\text{N}}::\overset{-}{\text{O}}:$  (53).

At  $-150^\circ\text{C}$ . the dichloro compound is more stable and nitric oxide takes a second atom of chlorine from it, giving a second molecule of nitrosyl chloride (59).

14. *Ionic reactions.* (a) *Electrolytes.* The electronic structure of electrolytes is so clearly recognized and their reactions have been so carefully studied that they need not be mentioned, further than to recall the unique character of the hydrogen ion discussed by Latimer and Rode-

bush (36). Because the hydrogen ion has no exterior electron it can approach the outer electrons of any negative ion, or, indeed of any other atom, more easily than any other positive ion can do this. For this reason acetic acid has a very low ionization constant, while that of sodium acetate is high. Probably a number of other chemical phenomena have the same reason.

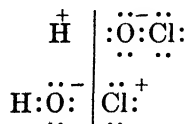
(b) Non-electrolytes. Van't Hoff (95) first demonstrated an ionic character for a reaction of a non-electrolyte by determining the stoichiometric relation between the amount of phosphorus oxidized and the amount of ozone formed when oxygen is in contact with moist phosphorus.

Jakowkin (24) demonstrated accurately, by means of partition experiments, that chlorine and water react in the dark to form hypochlorous and hydrochloric acids. An equilibrium between the four substances is very quickly reached, and the reaction is quantitatively reversible. The course of the experiment has all the usual characteristics of an ionic reaction, but Jakowkin did not suggest this explanation.

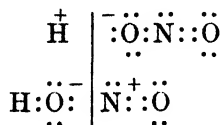
Two years later Stieglitz (85) interpreted Jakowkin's results by the ionic equation,



Twenty-two years later Noyes (51) suggested that this older, positive-negative theory is consistent with Lewis's theory if we assume that the two electrons of a covalence may remain together when the atoms separate in a chemical reaction. This suggestion has received strong support by the discovery that the electrons of a covalence have spins in opposite directions. According to this suggestion the atoms of a molecule of chlorine separate into  $\text{:}\ddot{\text{Cl}}^+$  and  $\text{:}\ddot{\text{Cl}}^-$ . Further support is given by the independent demonstration by Goldschmidt (16) and by Noyes and Wilson (69) that chlorine monoxide is present in the gaseous phase above the aqueous solution of hypochlorous acid. This is most simply explained by the relation,



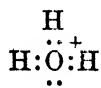
A similar relation for nitrous acid,



makes it possible to prepare alkyl nitrites quantitatively in a dilute aqueous solution (61).

In the same year that Stieglitz interpreted Jakowkin's reaction, Noyes and Lyon (66) and Lapworth (35) interpreted other reactions in a similar manner.

Ionic reactions furnish the simplest interpretation of a great variety of reactions. It is probable that many of these reactions occur through the immediate contact of the reacting compounds (48) or through the intervention of intermediate compounds. In cases where positive radicals with atoms having only six electrons are involved, these are, undoubtedly, ephemeral (60), as was demonstrated for positive chlorine by Noyes and Wilson in their study of hypochlorous acid (69). While this may be true and should be remembered in discussing reactions of this type, it seems impossible to deny that atoms and groups having the electronic structures given in this paper are actually transferred from one molecule to another and it is very convenient to use such formulas. It is altogether probable that hydrogen ions exist in aqueous solutions almost exclusively as positive oxonium ions,

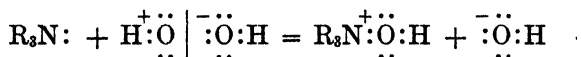


positive because the oxygen has three covalences. In writing reactions involving hydrogen ions no one thinks it necessary to represent them by this formula.

Organic chemists constantly use formulas for radicals which have never been isolated and which have odd electrons in the few cases where their independent existence has been demonstrated. It is a little difficult to see why so many chemists hesitate to use electronic formulas which have an even better basis than these formulas for radicals and which throw a clear light on the course of many reactions.

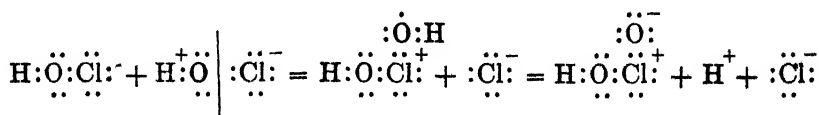
The following additional illustrations of ionic reactions of covalent compounds may be of service.

(1) The oxidation of a tertiary amine to the quaternary hydroxyammonium ion by hydrogen peroxide.



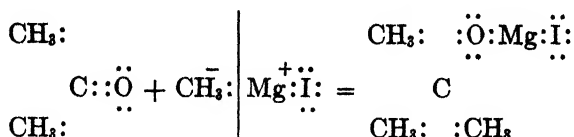
The separation of hydrogen peroxide into positive and negative hydroxyl (58) is similar to the separation of the chlorine molecule into positive and negative chlorine.

(2) The oxidation of hypochlorous acid to chloric acid by the positive hydroxyl from another molecule of hypochlorous acid (57);



This first step gives chlorous acid. A repetition gives chloric acid.

(3) The reaction of a Grignard reagent with an aldehyde or a ketone;



The magnesium, as a metal, allows the methyl to separate in the negative form carrying the pair of electrons. The positive radical,  $\text{Mg}^+:\ddot{\text{I}}:$ , then attaches itself to a pair of unshared electrons of the oxygen atom, causing that to become, momentarily, positive. This positive oxygen will then take a pair of covalence electrons from its double union with the carbon atom. This leaves the carbon atom positive, ready to combine with the negative methyl.

Water is a covalent compound but chemists find no difficulty in assuming the presence of hydrogen ions in alkaline solutions where the number of hydrogen ions must be excessively small. The assumption that hydrogen ions may separate from a carbon atom which is adjacent to another carbon atom which carries an oxygen atom, especially when the oxygen is in the semi-ionic condition characteristic of a sodium salt, enables us to account very simply for thousands of condensation reactions, e.g., for the Perkin, Kolbe, and Reimer-Tiemann reactions.

15. *Positive, neutral, and negative radicals.* From the discussions which have preceded this we may expect atoms and radicals to separate in three forms:

(1) Positive:  $\text{H}^+$  from water, acids, many compounds of carbon, ammonia, ammonium and their derivatives;  $\text{H}:\overset{\text{H}}{\underset{\text{H}}{\text{C}}}^+ \text{ from methyl iodide; } \ddot{\text{N}}::\overset{+}{\text{O}}$   
from nitrous acid;  $:\ddot{\text{Cl}}^+$  from molecular chlorine, from hypochlorous acid, and from nitrogen trichloride.

(2) Electrically neutral:  $\text{H}^{\cdot}$  in the Langmuir blowpipe, in the magnetic hydrogen atoms of Phipps and Taylor, and probably in the reactions of



molecular hydrogen in the presence of a catalyst;  $\ddot{\text{Cl}}$  in the thermal dissociation of chlorine (Victor Meyer) and probably in photochemical reactions and in the reaction of nitrogen trichloride with nitric oxide;  $\text{H}:\ddot{\text{C}}:$  from the electrolysis of sodium acetate and in thermal dissociations (Paneth, Rice).

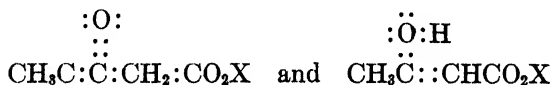
(3) Negative:  $\text{H}^-$  from the electrolysis of lithium hydride and in the mass spectra of Thomson; chloride ion,  $:\ddot{\text{Cl}}^-$  in the negative ion of hydrochloric acid;  $\text{Cl}_2\text{N}^-$  in the addition reactions of nitrogen trichloride (7); and  $\text{CH}_3^-$  in the reactions of the Grignard reagent.

It is difficult to express these relations satisfactorily without the use of dots to represent single and paired electrons, as was first proposed by Lewis.

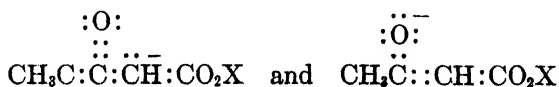
16. *Optical activity.* The tetrahedral dissymmetry of optically active compounds seems to be confirmed by the quantum mechanics studies of Pauling (72), which have been referred to. The optically active sulfonium compounds and the optically active sodium salts of aliphatic nitro compounds are of especial interest, because a pair of unshared electrons on a sulfur or on a carbon atom furnishes one of the four dissymmetric groups (21, 32, 78). See p. 14.

The static attraction between two ions in the same molecule which may hold the molecule in a stable cyclic configuration (68) when the ring contains six atoms does not do so when the ring would have seven atoms. The authors of the paper did not recognize, then, that the closure of the ring is due to an ionic valence and not to a covalence.

17. *Tautomerism.* It is now generally recognized that tautomerism is due to the existence of two isomers which have hydrogen atoms in different positions and with one or more double covalences which shift from one position to another. Occasionally there are labile methyl, phenyl, or other groups. For acetoacetic ester the two forms are:

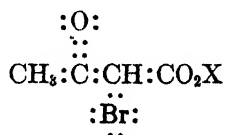


The shift of the hydrogen atom implies that it assumes the ionic form by leaving either the carbon or the oxygen. There are, therefore, two different ions:



In the first the pair of unshared electrons which give the negative character are on the carbon; in the second they are on the oxygen. When we recall that hydrogen attached to an oxygen atom ionizes easily in the presence of sodium and hydroxide ions, while hydrogen attached to carbon ionizes far less easily and usually leaves an ephemeral negative carbon atom having a pair of unshared electrons, it is evident that acids will favor the formation of the first form in an unionized condition and that alkalies will favor the formation of the second form (enol), in which the semi-ionic oxygen is balanced by metallic ions. These statements appear to the writer to be much more easily understood than the somewhat cumbersome terminology used by English authors.

Kurt Meyer (44) has shown that on treatment of the keto and enol forms of acetoacetic ester with bromine under suitable conditions the ketone is not affected but the enol is converted to the bromoacetoacetic ester,



Evidently the negative bromine atom from the bromine molecule unites with the labile hydrogen of the enol group, and one of the covalences between the two carbon atoms shifts to receive the positive bromine atom, while the pair to which the enol hydrogen was attached shifts to form a double covalence between the carbon and oxygen. The bromine atom combined with a carbon atom situated between two other carbon atoms, each of which is united to oxygen, may leave its covalence electrons with the carbon and separate in the positive form,  $\text{:Br:}^+$ . In this form the

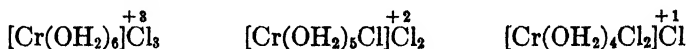
bromine will take the hydrogen and a pair of electrons from two molecules of hydriodic acid, liberating free iodine. One atom of the hydrogen replaces the positive bromine and regenerates the original acetoacetic ester in the keto form. The other hydrogen atom remains as an ion to balance the bromine, which has become negative by accepting the pair of electrons taken from the iodine when two iodide ions become free iodine.

The induced polarity of the carbon atom between two carbonyl groups is similar to the induced polarity of the oxygen of acetic acid produced by a chlorine atom in the  $\alpha$ -position, increasing the ionization constant of the acid.

Hydrocyanic acid exists in two tautomeric forms,  $\text{H:C::N:}$  and  $\text{:C::N:H}$  (94). Removal of hydrogen from either form leaves the same negative ion,  $\text{:C::N:}^-$ . Because of the mobility of the hydrogen ion the two forms are in equilibrium, with the first form in very large excess.

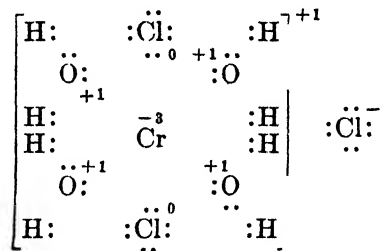
As often happens in similar cases, replacement of the hydrogen by phenyl or other groups gives two different compounds, phenyl cyanide,  $C_6H_5:C::N:$ , which is easily hydrolyzed to benzoic acid and ammonia, and phenyl isocyanide,  $C_6H_5:N::\overset{+}{C}:$ , which may be oxidized to phenyl isocyanate and hydrolyzed to aniline and a carbonate. The electronic structure of the isomers has been quite conclusively determined by means of the parachors, dipole moments, and other properties (20).

18. *Coördination.* Many years ago Werner discovered that atoms and molecules may be combined with a central metallic atom in different ways. For example, there are three hydrates of chromic chloride,



In the first all the chlorine ionizes and may be precipitated by silver nitrate; in the second two-thirds, and in the third only one-third can be precipitated. Werner called the chlorine and water within the brackets "coördinated."

Sidgwick (80) threw a flood of light on the nature of these compounds when he suggested that the coördinated atoms and groups are held to the central atom by covalences. According to this, the electronic structure of the third compound is



Sidgwick introduced the terms "donor" and "acceptor" in connection with the covalences of coördinate compounds and called such a covalence a "coördinate link." He recognized that the central atom, which is the acceptor, increases its negative charge, but not so clearly that the chloride ions and water increase their positive charges exactly as ammonia increases its positive charge when it is donor to a hydrogen ion (see p. 13). He seems to overlook the fact that each covalence must balance two positive unit charges situated in the nuclei of two *different* atoms. While the negative charges of the two covalent electrons may not be equally distributed, good reasons have been given earlier in this paper for thinking that they are approximately so distributed, and this gives us a very simple method for estimating the distribution of the charges within the complex. The chromium kernel has a positive charge of three units. The chlorine atoms

enter the complex as negative ions, not as neutral atoms, as Sidgwick has supposed.

As donors, these two negative ions become electrically neutral and the chromium atom, as an acceptor, acquires two negative charges from the two chlorine atoms. The four molecules of water enter the complex as neutral molecules, and as donor each acquires a positive charge, as ammonia acquires a positive charge when it unites with a hydrogen ion. The chromium as acceptor of the four molecules of water acquires four negative charges, a total of six in all. Three of the six are balanced by the three positive charges of the chromium kernel, three are balanced by three of the positive oxonium groups, leaving one positive charge for the complex as a whole. This positive charge is balanced by the external chloride ion (62). No matter how the charges may be distributed between the chromium kernel, the water molecules, and the chlorine atoms within the complex, this net result must be true for the complex as a whole. The net result is, of course, the same as that of Sidgwick (82).

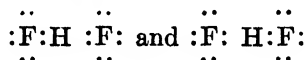
There is a fourth chromic chloride hydrate, because the form with two coördinated chlorine atoms has a *cis-trans* isomerism. A fifth form with all three chlorine atoms coördinated is theoretically possible. These forms do not affect the principles which determine the positive or negative character of the atoms and groups within the complex and the ionic charge of the complex when there are exterior ions.

Sidgwick defines a coördinate link as one in which one of the atoms furnishes the two electrons for a covalence. This overlooks the fact that a covalence is the same, when once formed, when one of the atoms furnishes the pair as when each atom furnishes one of the pair. Water is the same when it is formed by the union of a hydroxide ion with a hydrogen ion as when it is formed by burning hydrogen in oxygen. When a hydrogen ion combines with ammonia to form an ammonium ion, it becomes identical with the three hydrogen atoms coming from the ammonia. It was at this point that Werner's discussion of ammonium salts was not satisfactory.

A definition of coördination should not emphasize the manner in which the covalences are formed. The two characteristics of most importance are: (1) A coördinated atom has, usually, a larger number of covalences than the number of positive units in its kernel charge. Silicon is coördinated in the fluosilicate ion,  $\text{SiF}_6^-$ , in which the silicon atom has six covalences. (2) When the pair of electrons for a covalence is furnished by one of the atoms or by a neutral molecule the donor increases its positive charge and the acceptor its negative charge. The negative charge of the fluosilicate ion is due to the fact that a silicon atom which has four positive units in its kernel charge has six covalences.

In a paper published two years ago (63) I used the coördinate for-

formula  $\begin{array}{c} \cdot\cdot & - & \cdot\cdot \\ \text{H}:\text{F}:\text{H}:\text{F}: \end{array}$  for bimolecular hydrofluoric acid. Sidgwick had previously used the same formula (81). The chemical evidence points strongly to such a conclusion, especially the well-known fact that  $\text{H}_2\text{F}_2$  is a bibasic acid forming well-defined salts of the type  $\text{KHF}_2$ , the very low ionization constant, and the association in the gaseous state at ordinary temperatures. Abegg (2) states that the acid is ionized only to the extent of 15 per cent in a normal solution and that five-sixths of the ionization is to  $\text{H}^+$  and  $\text{F}_2\text{H}^-$ . These facts indicate that the ion  $\text{F}_2\text{H}^-$  is a well-defined complex having properties similar to those of coördinate compounds and more stable than many of these. These chemical facts are most simply explained by assuming that the group is a covalent one, the hydrogen having two covalences and the two fluorine atoms being electrically neutral as they are in silicon tetrafluoride and in the fluosilicate ion. Silicon tetrafluoride has, almost certainly, a tetrahedral covalence shell of electrons, while the analogy from compounds studied by Werner indicates an enlarged octahedral covalence shell for  $\text{SiF}_6^{--}$ . It does not seem unreasonable to think that hydrogen might have an enlarged covalent shell with four electrons. However, both Mulliken and Pauling think this impossible or, at least, extremely improbable and Sidgwick is of the same opinion (83a). Pauling and Sidgwick think there may be a "resonance" between



Important advances have been made in the study of electronic structures during the past decade by de Broglie, Pauli, Heisenberg, Born and Jordan, Dirac, Goudsmit and Uhlenbeck, Schrödinger, Davisson and Gerner, Mulliken and Pauling. I am not competent to discuss these advances in detail and could not hope to add to the very illuminating paper by Lewis (41).

I wish to express appreciation of my indebtedness to Professors Sidgwick, Lowry, W. Albert Noyes, Mulliken, Pauling, and Stieglitz, who have read this paper and offered many valuable suggestions. It will be understood, of course, that we are not entirely agreed about some points, but it is hoped that this attempt will help to clarify our ideas and contribute toward a unification of electronic theories.

#### REFERENCES

- (1) ABEGG: *Z. anorg. Chem.* **39**, 330 (1904).
- (2) ABEGG: *Handbuch der anorganischen Chemie*, IV, **2**, p. 40. S. Hirzel, Leipzig (1927).
- (3) ANDERSON: *Phys. Rev.* **43**, 491 (1933).
- (4) BERZELIUS: *Schweigger's J.* **6**, 119 (1812).
- (5) BOHR: *Phil. Mag.* **26**, 1, 476, 857 (1913).

- (6) CAMPBELL, N. R.: *Nature* **111**, 569 (1923).
- (7) COLEMAN AND HOWELLS: *J. Am. Chem. Soc.* **45**, 3084 (1923).
- (8) CROOKES: *Chem. News*, 1879-80.
- (9) DAVY: *Phil. Trans.*, p. 1 (1807).
- (10) EINSTEIN: *Ann. Physik* **17**, 891 (1905).
- (11) EINSTEIN: *Ann. Physik* **18**, 641 (1905).
- (12) EINSTEIN: *Ann. Physik* **22**, 180 (1907).
- (13) FARADAY: *Phil. Trans.* **55**, 77 (1834); *Pogg. Ann.* **33**, 149, 433, 481 (1834).
- (14) GERLACH AND STERN: *Z. Physik* **9**, 349, 353 (1922).
- (15) GLOCKLER: *J. Am. Chem. Soc.* **48**, 2021 (1926).
- (16) GOLDSCHMIDT: *Ber.* **52**, 755 (1919).
- (17) GOMBERG: *J. Am. Chem. Soc.* **22**, 757 (1900); **23**, 496 (1901).
- (18) GOUDSMIT AND UHLENBECK: *Nature* **117**, 264 (1926).
- (19) HAHN, GEORG: *Homoöpolare Bindung*. Johann Wolfgang Goethe University, Frankfurt-on-Main. See review in *J. Am. Chem. Soc.* **57**, 965 (1935).
- (20) HAMMICK, NEW, SIDGWICK, AND SUTTON: *J. Chem. Soc.* **1930**, 1876.
- (21) HARRISON, KENYON, AND PHILLIPS: *J. Chem. Soc.* **1926**, 2079.
- (22) HELMHOLTZ: Faraday lecture, *J. Chem. Soc.* **39**, 277 (1881).
- (23) INGOLD: *J. Chem. Soc.* **1928**, 904; **1929**, 8; **1931**, 1666, and many other papers.
- (24) JAKOWKIN: *Z. physik. Chem.* **29**, 613 (1899).
- (25) KAUFMANN: *Ann. Physik* **61**, 544 (1897).
- (26) KHARASCH: *J. Am. Chem. Soc.* **55**, 2468 (1933).
- (27) KNORR, C. A.: *Z. anorg. Chem.* **129**, 109 (1923).
- (28) KOLBE: *Ann.* **69**, 279 (1849).
- (29) KOPP: *Ann.* **96**, 328 (1855).
- (30) KOSSEL: *Ann. Physik* **49**, 229-362 (1916); *Naturwissenschaften* **7**, 339, 360 (1919).  
The book by van Arkel and de Boer, *Chemische Bindung als elektrostatische Erscheinung* (translation by Klemm and Klemm, S. Hirzel, Leipzig, 1931), gives an excellent detailed exposition of Kossel's theory.
- (31) KOSSEL: *Naturwissenschaften* **7**, 339-45, 360-6 (1919); *Z. Physik* **1**, 395-415 (1920).
- (32) KUHN AND ALBRECHT: *Ber.* **60**, 1297 (1927).
- (33) KUNZ, TAYLOR, AND RODEBUSH: *Science* **63**, 550 (1926).
- (34) LANGMUIR: *J. Am. Chem. Soc.* **41**, 868, 1543 (1919); *Science* **54**, 59 (1921).
- (35) LAPWORTH: *J. Chem. Soc.* **79**, 1267 (1901).
- (36) LATIMER AND RODEBUSH: *J. Am. Chem. Soc.* **42**, 1424 (1920).
- (37) LEWIS: *J. Am. Chem. Soc.* **38**, 765 (1916).
- (38) LEWIS: *J. Am. Chem. Soc.* **38**, 778 (1916).
- (39) LEWIS, G. N.: *J. Am. Chem. Soc.* **38**, 762 (1916); *Valence and the Structure of Atoms and Molecules*, American Chemical Society Monograph (1923); *The Nature of the Chemical Bond*, *J. Chem. Physics* **1**, 17 (1933).
- (40) LEWIS: *Valence and the Structure of Atoms and Molecules*, American Chemical Society Monograph, p. 29. The Chemical Catalog Co., Inc., New York (1923).
- (41) LEWIS: *J. Chem. Physics* **1**, 17 (1933).
- (42) LOWRY: *J. Chem. Soc.* **123**, 822 (1923); *Trans. Faraday Soc.* **18**, 285 (1933); **19**, 488 (1933).
- (43) MAXWELL: See review in *Nature* **7**, 478 (1873).
- (44) MEYER, KURT: *Ann.* **380**, 212 (1911).
- (45) MICHELSON AND MORLEY: *Am. J. Sci.* **31**, 377 (1886); **34**, 333 (1887).
- (46) MORLEY AND MILLER: *Am. Acad. Arts Sci.* **41**, 321 (1905).

- (47) MOSELEY: *Phil. Mag.* **26**, 1024 (1913); **27**, 703 (1914).  
(48) NOYES: *Chem. News* **90**, 228 (1904); *Science* **20**, 490 (1904).  
(49) NOYES: *J. Am. Chem. Soc.* **34**, 663 (1912).  
(50) NOYES: *J. Am. Chem. Soc.* **39**, 879 (1917).  
(51) NOYES: *J. Am. Chem. Soc.* **45**, 2959 (1923).  
(52) NOYES: *J. Am. Chem. Soc.* **47**, 3027 (1925).  
(53) NOYES: *J. Am. Chem. Soc.* **50**, 2902 (1926).  
(54) NOYES: *Proc. Nat. Acad. Sci.* **13**, 377 (1927). In that paper the magnetic character was ascribed to the rotation.  
(55) NOYES: *J. Am. Chem. Soc.* **51**, 2392 (1929). Also reference 67, p. 107.  
(56) NOYES: *Z. physik. Chem.* **130**, 327 (1927); *J. Am. Chem. Soc.* **51**, 2393 (1929).  
(57) NOYES: *J. Am. Chem. Soc.* **51**, 2393 (1929).  
(58) NOYES: *J. Am. Chem. Soc.* **51**, 2394 (1929).  
(59) NOYES: *J. Am. Chem. Soc.* **52**, 4298 (1930).  
(60) NOYES: *J. Am. Chem. Soc.* **55**, 657 (1933).  
(61) NOYES: *J. Am. Chem. Soc.* **55**, 3888 (1933).  
(62) NOYES: *J. Am. Chem. Soc.* **55**, 4889 (1933).  
(63) NOYES: *J. Am. Chem. Soc.* **55**, 4892 (1933).  
(64) NOYES: *J. Am. Chem. Soc.* **55**, 4893 (1933).  
(65) NOYES: *Ind. Eng. Chem., News Edition* **12**, 378 (1934).  
(66) NOYES AND LYON: *J. Am. Chem. Soc.* **23**, 463 (1901).  
(67) NOYES AND NOYES: *Modern Alchemy*, p. 98. Thomas, Springfield (1932).  
(68) NOYES AND POTTER: *J. Am. Chem. Soc.* **37**, 189 (1915).  
(69) NOYES AND WILSON: *J. Am. Chem. Soc.* **44**, 1630 (1922).  
(70) PANETH AND HOFEDITZ: *Ber.* **62**, 1335 (1929).  
(71) PARSON: *Smithsonian Institution Publications* **65**, No. 11 (1915).  
(72) PAULING: *J. Am. Chem. Soc.* **53**, 1378 (1931).  
(73) PHIPPS AND TAYLOR: *Science* **64**, 480 (1926).  
(74) PLANCK: *Ann. Physik* **4**, 553 (1901).  
(75) RICE, F. O.: *J. Am. Chem. Soc.* **53**, 1959 (1931).  
(76) RICE, JOHNSTON, AND EVERING: *J. Am. Chem. Soc.* **54**, 3529 (1932).  
(77) RUTHERFORD: *Phil. Mag.* **21**, 669 (1911).  
(78) SHRINER AND YOUNG: *J. Am. Chem. Soc.* **52**, 3332 (1930).  
(79) SIDGWICK: *Trans. Faraday Soc.* **19**, 469 (1923).  
(80) SIDGWICK: *J. Chem. Soc.* **123**, 725 (1923); *The Electronic Theory of Valency*, pp. 60, 109-31. Clarendon Press, Oxford (1927).  
(81) SIDGWICK: *The Electronic Theory of Valency*, p. 72.  
(82) SIDGWICK: *The Electronic Theory of Valency*, p. 114.  
(83) SIDGWICK: *The Electronic Theory of Valency*, p. 116.  
(83a) SIDGWICK: *Annual Reports of the Chemical Society*, 1933, p. 112.  
(84) SLATER, J. C.: *Phys. Rev.* **37**, 481 (1931).  
(85) STIEGLITZ: *J. Am. Chem. Soc.* **23**, 797 (1901).  
(86) STIEGLITZ: *J. Am. Chem. Soc.* **44**, 1293 (1922).  
(87) SUGDEN: *J. Chem. Soc.* **125**, 1177 (1924).  
(88) SUGDEN: *J. Chem. Soc.* **127**, 1527 (1925).  
(89) SUGDEN: *J. Chem. Soc.* **127**, 2556, 2570 (1925).  
(90) TAYLOR: *Phys. Rev.* **28**, 576 (1926).  
(91) TAYLOR: *Phys. Rev.* **29**, 309 (1927).  
(92) THOMSON: *Phil. Mag.* **44**, 293 (1897).  
(93) THOMSON: *Phil. Mag.* **7**, 237 (1904).  
(94) USHERWOOD: *J. Chem. Soc.* **121**, 1604 (1922).  
(95) VAN'T HOFF: *Z. physik. Chem.* **16**, 411 (1895).

# PROPERTIES OF ELECTROLYTIC SOLUTIONS<sup>1</sup>

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## I. INTRODUCTION

The most general problem in the theory of solutions may be formulated as follows: Given a homogeneous mixture of several substances of known chemical composition, what are the properties of the solution as functions of temperature, pressure, concentration, and parameters describing external forces? The phrase "of known composition" implies, of course, that parameters characteristic of the various components will appear in the final result. In principle, these should be reducible to atomic and molecular constants. It is, in general, possible to express any property as a function of any variable by means of empirical equations based on accurate experimental data, but, while such a result serves to correlate measurements on various phenomena, it may not be considered as a solution of the problem. A satisfactory solution of the problem will be one in which all constants have an assignable physical significance (which may perhaps be fictitious; we must, however, require at least a one to one correspondence between model and fact), and in which the mathematical form of the functions is predicted on the basis of reasonable theoretical arguments.

It is the purpose of the present paper to consider a very restricted phase of the general problem,—the properties of dilute solutions of binary electrolytes. Unsymmetrical electrolytes are excluded for the sake of mathematical simplicity. Furthermore, those electrolytes which form true neutral molecules by electron rearrangement of the constituent ions after contact are excluded from discussion, because so little is known of their properties. (It is true that weak acids, for example, have been extensively investigated in aqueous solution, but these represent too special a case to permit generalization.)

Among the various measurable properties of electrolytic solutions, the conductance is probably the one which can be measured with the highest precision over the widest range of all of the physical variables. For

<sup>1</sup> This paper was read at the Ninetieth Meeting of the American Chemical Society, at San Francisco, August 20, 1935, on the occasion of the presentation of the American Chemical Society Award in Pure Chemistry for 1935.



practical purposes, therefore, we shall base most of our examples and arguments on conductance data. One fundamental difference between conductance and thermodynamic properties should perhaps be emphasized; the former represents an irreversible process, while the latter are (or at least, should be) measured by means of reversible processes. A satisfactory theory of electrolytes must be able to account for both types; unfortunately, very few data on thermodynamic properties of electrolytes in non-aqueous solvents are available at present for comparison with theory, and again the abundance of data on aqueous solutions has served primarily to obscure the general problem, inasmuch as conclusions based on a special limiting case (solvent of high dielectric constant) cannot be extrapolated into regions where entirely different microscopic phenomena appear.

On the basis of well-known general principles, it is possible to derive all of the properties of a solution from its free energy and this, in turn, by means of the phase integral, from the total energy which is the sum of the individual energies of the solute particles. These energies depend, finally, on the relative positions of the solute particles, so that the problem resolves itself fundamentally into the question of the relative location of the ions, assuming, of course, that we know the laws of force as a function of distance. The actual solution of the problem directly through the phase integral<sup>2</sup> involves a number of mathematical difficulties, most of which are yet to be overcome. It is possible, however, to obtain an approximate solution of the problem by considering the distribution of the ions in an electrolytic solution, and then treating various ions in different ways, according to the relative magnitudes of the terms in the total energy of each ion. This approximate treatment will be the subject of the present paper; the distribution of ions in solution will be investigated and it will be shown that it is possible to split interionic effects into long and short range interactions. The former may be treated by the time average method of Debye and Hückel (5) and the latter by the formal methods of dissociation theory. Based on these results, equations will be derived which quantitatively reproduce experimental data on conductance for dilute solutions of ordinary electrolytes in all solvents so far investigated. Various limitations to the treatment will be pointed out.

## II. IONIC DISTRIBUTION

Any theoretical calculation of physical properties meets at the very beginning the necessity for a series of arbitrary assumptions, because an

<sup>2</sup> Kirkwood (19) has presented a very careful analysis of the problem for the case of strong electrolytes and has suggested, in section IV of his paper, an alternative to the method presented here for handling association.

idealized and simplified model must be chosen to represent the actual physical system under consideration. Inevitably, parameters with the dimensions of distance appear; within certain limits, we may ascribe to them the nature of molecular dimensions, but as a matter of fact, they represent the dimensions of a fictitious particle in a hypothetical medium, the two so chosen that the idealized system will duplicate the properties of the real system when a given variable is changed. For the present discussion, we shall use the conventional model: the ions are assumed to be uniformly charged spheres (charges  $\pm e$ ) of diameter  $a$  in a homogeneous medium which is completely described electrically by its macroscopic dielectric constant and hydrodynamically by its macroscopic viscosity. Interaction between solvent and solute is excluded; solvation, which may mean actual complex ion formation, or simply electrostatic dipole saturation, is absorbed in the assumption that the size of the ion in solution may be larger than that of the lattice ion. The dielectric constant is assumed to be a true constant, although the effective dielectric constant between two real ions at short distances is presumably much smaller than  $D$ , the macroscopic dielectric constant.<sup>3</sup> Furthermore, the ion is assumed to be rigid mechanically and also unpolarizable, so that all forces of repulsion are approximated by a potential which becomes positively infinite at  $r = a$ . Electron rearrangement is completely neglected in this model, and quantized bonds are, of course, entirely excluded from discussion. The assumption of spherical symmetry of charge distribution in the model is also a special restriction.<sup>4</sup>

These and other recognized imperfections of the model described above may, in principle at least, be eliminated by more elaborate mathematical methods, but for the present we shall use the simple model.

We consider then a solution containing  $N$  ions of charge  $+e$  and  $N$  ions of charge  $-e$  in a total volume  $V$ . The contribution to the free energy due to electrostatic forces is given by the equation

$$e^{-F/kT} = V^{-2N} \int \dots \int e^{-E/kT} (dV)^{2N} \quad (1)$$

where the total electrostatic potential energy may be written

$$E = \frac{1}{2} \sum_{ij}' u_{ij} \quad (2)$$

<sup>3</sup> Very interesting and suggestive results are obtained by setting  $D = D(r)$ , where  $r$  is the distance between two ions. The function  $D(r)$  is probably an  $S$ -function, which may be approximated by a step function:  $D(r) = 1$ ,  $a \leq r \leq a + a'$ ;  $D(r) = n^2$ ,  $a + a' \leq r \leq d$ ;  $D(r) = D$ ,  $d \leq r < \infty$ , where  $d$  is a distance equal in order of magnitude to the distance from an ion at which a solvent dipole of strength  $\mu$  has an even chance of assuming a random orientation, i.e., where  $\epsilon\mu/r^2 D(r) kT = 1$ .

<sup>4</sup> Kirkwood (18) has discussed a model in which the ionic charge distribution is arbitrary, and has applied his results to the case of zwitterions.

if  $u_{ij}$  represents the mutual energies of ions  $i$  and  $j$ . For the  $i^{\text{th}}$  ion, we have as its total potential energy

$$E_i = u_{i1} + u_{i2} + \cdots + u_{i,i-1} + u_{i,i+1} + \cdots + u_{i,2N} \quad (3)$$

Now many terms of  $E_i$  may be entirely negligible compared to  $kT$ , because

$$u_{ij} = \epsilon_i \epsilon_j / Dr_{ij} \quad (4)$$

and  $r_{ij}$  has as its maximum value a distance of the order of  $V^{1/3}$ . In fact,  $u_{ij}$  will converge to zero much faster than  $1/r$ , because, if we anticipate somewhat, the electrostatic screening due to ions between  $i$  and  $j$ , when  $r_{ij} \gg a$ , will lead to a potential

$$\psi_i = \epsilon_i e^{-\kappa r} / Dr \quad (5)$$

around the  $i^{\text{th}}$  ion, thus multiplying the Coulomb  $1/r$  potential by a negative exponential. For practical purposes, we could approximate the sum (equation 3) very closely by neglecting all terms  $u_{ij}$  for which  $r_{ij}$  was greater than say six or a dozen times  $1/\kappa$ . Now in the remaining terms, we may expect to find several relative orders of terms. If no particular ion  $j$  happened to be near (i.e.,  $r \approx a$ ) ion  $i$  in the configuration selected, many of the terms  $u_{ij}$  would be of equal magnitude, although smaller than  $kT$ . On the other hand, we might find one particular ion  $j = k$ , such that  $r_{ik} \approx a$ , in which case  $u_{ik}$  would be much larger than all the other terms of  $E_i$ . This term would then control the contribution of ion  $i$  to  $F$ . Another case would be when two ions  $l$  and  $m$  were near  $i$ , so that  $(u_{il} + u_{im})$  would make up the main contribution to  $E_i$ . Even in the first case (many  $u_{ij}$ 's approximately equal), we should be able to select one term which was larger than the others, although perhaps only infinitesimally so. We are thus led to seek a classification of the ions which will permit an ordering of their energies in sequences, such that the largest term (which may also be the leading term) of  $E_i$  can be selected.

Let us consider a particular instantaneous configuration of the ions in the total volume  $V$ , which temporarily will be chosen so large that groups containing three ions at distances of the order of  $a$  will be negligibly rare. Let each positive ion be surrounded by a concentric sphere of radius  $a/2$ , and then let all the spheres expand at a uniform rate, until a distance of the order of  $V^{1/3}$  is reached. As soon as the sphere for a given positive ion cuts the center of a negative ion, we shall count these two ions as a pair, provided that the negative ion has not already been counted at some smaller distance as the partner of some other positive ion. In this way, we are able to assign a unique partner to each positive ion, namely, that negative ion which is nearest to the central ion, provided that the former ion is not

nearer to some other positive ion than to the reference positive ion. If the nearest ion has already been assigned to a partner, then the next nearest is counted, and so on. We may define an ion pair of this type as follows: a positive ion and a negative ion, the center of which lies in  $dr$  at a distance  $r$  from the positive ion are counted as an ion pair, provided that no other unpaired negative ion lies within a sphere of radius  $r$  drawn around the positive ion (7).

The probability  $G(r)dr$  for such a configuration is proportional to  $4\pi r^2 dr/V$ , the ratio to the total volume of the volume which is to contain the partner ion; to  $N$ , the total number of negative ions present; to the Boltzmann factor,  $\exp(\epsilon^2/DkT)$ ; and to the probability  $f(r)$  that an unpaired ion is not already in the sphere  $4\pi r^3/3$ . The chance that another ion at  $x$ ,  $a \leq x \leq r$ , should have been counted as the partner of the central ion is  $[(N-1)/N] G(x)dx$ , and the probability that no such ion is anywhere in the sphere  $4\pi r^3/3$  is

$$f(r) = 1 - \frac{N-1}{N} \int_a^r G(x)dx \quad (6)$$

giving the following integral equation for  $G(r)$ :

$$G(r) = \frac{4\pi N}{V} r^2 e^{\beta/r} \left( 1 - \frac{N-1}{N} \int_a^r G(x)dx \right) \quad (7)$$

where

$$\beta = \epsilon^2/DkT \quad (8)$$

The solution of equation 7 is

$$G(r) = \frac{4\pi N}{V} r^2 \exp \left( \frac{\beta}{r} - \frac{4\pi N}{V} \int_a^r e^{\beta/x} x^2 dx \right) \quad (9)$$

We note that

$$\int_a^\infty G(r) dr = 1 \quad (10)$$

The above derivation contains the approximation that the potential around the central ion is  $\epsilon^2/Dr$ ; in other words, the screening effects due to possible ions between the two ions of the pair, which would cause the insertion of a factor  $\exp(-\kappa r)$ , are neglected. This approximation is not serious for our present purpose, because the function will be used primarily to classify the ions into several groups, and the general character of  $G(r)$  for this purpose is not changed by inserting the correction factor.

As a function of  $r$ ,  $G(r)$  may have two peaks. If we assume low concentrations, and have

$$b = \epsilon^2/aDkT > 2 \quad (11)$$

the first is an exponential peak at  $r = a$  and the second is a maximum at a distance

$$\rho = \sqrt[3]{V/2\pi N} (1 - \beta \sqrt[3]{V/2\pi N} + \dots) \quad (12)$$

which is in order of magnitude the distance between uniformly distributed particles.

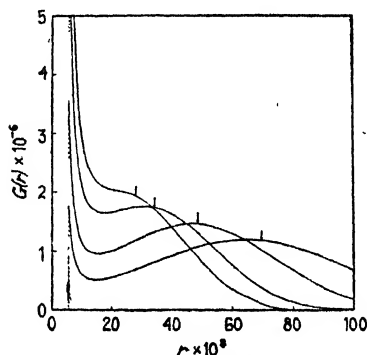


FIG. 1. Distribution curves for  $c = 5, 10, 20$ , and  $30 \times 10^{-4}$ ,  $a = 5.57 \times 10^{-8}$ ,  $D = 20$ ,  $t = 25^\circ\text{C}$ . Arrows mark the distance  $1/\kappa$ .

Between  $r = a$  and  $r = \rho$  is a minimum which comes approximately at the Bjerrum radius

$$q = \epsilon^2/2DkT = \beta/2 \quad (13)$$

Up to  $r = \beta/2$ , the function  $G(r)$  approximates the Bjerrum distribution function; beyond  $r = \beta/2$ ,  $G(r)$  resembles roughly the distribution curve for a pairwise selection of uncharged particles.

An example of the distribution curve is given in figure 1, where  $D = 20$ ,  $t = 25^\circ\text{C}$ ,  $a = 5.57 \times 10^{-8}$ ,  $\beta = 27.8 \times 10^{-8}$ , and  $c = 5, 10, 20$ , and  $30 \times 10^{-4}$ . If we consider only the lower concentrations, we find that the ions present may be divided into several groups: those which find partners near  $r = a$ , those with partners near  $r = \beta/2$ , and those with partners near  $r = \rho$ . (In view of the definition of  $G(r)$ , the fraction of all the positive ions which find partners between  $r_1$  and  $r_2$  is obviously

$$\int_{r_1}^{r_2} G(r) dr$$

i.e., the area under  $G(r)$  between  $r_1$  and  $r_2$ ; cf. equation 10.) The group for which  $r \approx \beta/2$  will represent a small fraction of the total, because they correspond to a *minimum* probability; the ions in this group are ions in

transition from short to long range pairs, through the probability barrier at  $r \approx \beta/2$ .

The ions in the short range pairs are ions which are near together on account of Coulomb attraction. By far the largest term in their total potential energy is the contribution from their mutual interaction. Their net external field, as far as other ions are concerned, is essentially a dipole field, which corresponds to a  $1/r^2$  energy. Compared to the  $1/r$  energies of ion-ion interaction, we are led to neglect in first approximation the interaction of ions in such short range pairs with ions at large distances from either. In other words, we count ions in short range pairs as associated, as was first suggested by Bjerrum (3), and assume them to act approximately like single particles of an ideal solute. If we assume that ions for which  $a \leq r \leq d$  are associated, where  $d$  is a distance<sup>5</sup> of the order of several times  $a$  and has its upper limit  $\beta/2$ , then the fraction of solute associated is given by

$$1 - \gamma = \int_a^d G(r) dr = 1 - \exp\left(-\frac{4\pi N}{V} \int_a^d e^{\beta/r} r^2 dr\right) \quad (15)$$

In the limit of zero concentration, we have

$$\lim_{c \rightarrow 0} \frac{1 - \gamma}{c} = \frac{4\pi L}{1000} \int_a^d e^{\beta/r} r^2 dr \quad (16)$$

Now if we had a mass action equilibrium between free and associated ions of the type



the left side of equation 16 defines the reciprocal of the mass action constant  $K$  for equation 17, and the right side of equation 16 evaluates  $K^{-1}$  in terms of parameters characteristic of solvent and solute.

The ions in the long range pairs (those whose partner is found at distances of the order of  $\rho$ ) must be treated in a different way. Here the interaction with all the neighboring ions (except with those in short range pairs within the present approximation) rather than with merely the nearest

<sup>5</sup> For a discussion of  $d$ , see reference 7. As a matter of fact, the association calculated is not very sensitive to the value of  $d$  on account of the exponential peak in  $G(r)$  at  $r = a$ . For practical purposes, it is sufficient to choose  $d$  equal to two or three times  $a$ ; or, for the sake of uniformity with earlier work, to take  $d = \beta/2$ . Halpern's objections (J. Chem. Physics 2, 85 (1934)) to the latter choice are unfounded; the

proper volume to exclude as belonging to ion pairs is  $(4\pi/3) \int_a^d r^3 G(r) dr$ , and the ratio

of this to  $V$  is always small in the range of concentration over which the equations derived from  $G(r)$  apply. The "thermodynamic" objection is likewise groundless, because the free energy of a single ion pair has no more meaning than the temperature of a single molecule.

ion of opposite charge must be taken into account. A simple calculation shows that

$$\epsilon^2/\rho DkT \ll 1 \quad (18)$$

when the concentration is small, so that the potential energy of an ion in this group with respect to the nearest otherwise unpaired ion is small compared to the energy of thermal motion. There will be in its potential energy many terms of the same order of magnitude all of which, however, are small. This situation suggests that a time average treatment be applied to the calculation of the mutual energy of ions in long range pairs, and we are naturally led to the Poisson-Boltzmann equation derived by Debye and Hückel. Fluctuation terms are due to ions for which  $r \approx \beta/2$ ; their effects are negligible at low concentrations (8). The ions for which  $r \approx a$ , and which would represent very serious fluctuation terms in any time average treatment, are handled separately by means of the association hypothesis.

On the basis of the distribution function  $G(r)$ , we have thus divided the ions in solution into three groups: short range pairs or associated ions, long range pairs or free ions, and ions in transition. The latter group will always represent a small fraction of the total at low concentrations, and for the sake of simplicity may be included with the free ions, which will then be defined as all ions whose distance to the nearest unpaired ion of opposite sign is greater than  $d$ , a distance equal to several ionic diameters. Furthermore, we have seen that, according to equation 16, the relative concentrations of free and bound ions satisfy the formal laws of dissociation theory. Let us now calculate the conductance as a function of concentration. The total current  $i$  for unit field between unit electrodes is given by the product of the number of conducting ions per unit volume times charge times mobility. If we assume that a fraction  $(1 - \gamma)$  of the total solute is associated and hence non-conducting for direct current, we have

$$i = Fc\gamma(v_+ + v_-)/1000 \quad (19)$$

where  $F = 96,494$  coulombs,  $c$  = concentration in equivalents per liter, and  $v$  is mobility. The mobility of the free ions at finite concentrations is less than  $v^0$ , the limiting mobility, on account of long range interionic effects, and it has been shown (24) that for low free ion concentrations,

$$v = v^0 - A\sqrt{c} \quad (20)$$

Combining equations 19 and 20 and recalling the definition of equivalent conductance,  $\Lambda$ , we have

$$\Lambda = \gamma(\Lambda_0 - \alpha\sqrt{c\gamma}) \quad (21)$$

where  $\alpha$  is the Onsager coefficient and  $\Lambda_0$  is the limiting conductance. Equation 21 represents a combination of two effects which can change  $\Lambda$  with changing concentration; both the actual relative number of conducting particles, as well as their mobilities, are assumed to be functions of concentration. The equation thus combines the original ideas of Arrhenius with the modern notions of interionic forces.

If we know  $\Lambda_0$  and  $\alpha$  and measure  $\Lambda$  as a function of  $c$ , equation 21 permits us to determine  $\gamma$ , the "degree of dissociation," as a function of  $c$ . Formally, we can solve equation 21 for  $\gamma$  by the usual algebraic methods, but a slight transformation gives a much more convenient form. If we define a new variable  $z$  by the relation

$$z = \alpha \Lambda_0^{-3/2} \sqrt{c\Lambda} \quad (22)$$

we find

$$\Lambda = \gamma \Lambda_0 F(z) \quad (23)$$

where

$$F(z) = \frac{4}{3} \cos^2 \frac{1}{3} \cos^{-1}(-3 \sqrt{3} z/2) \quad (24)$$

$$= 1 - z(1 - z(1 - z(1 - \dots)^{-1/2})^{-1/2})^{-1/2} \quad (25)$$

The function  $F(z)$  has been calculated (11) and tabulated for a series of values  $0 \leq z \leq 0.209$ . Consequently, the solution of equation 21 for  $\gamma$ , given  $\alpha$ ,  $\Lambda_0$ ,  $\Lambda$ , and  $c$  can be carried out very simply. But obtaining numerical values for  $\gamma$  does not furnish a test of the equation; rather it is necessary to find some other relationship which  $\gamma$  must satisfy, and then to make the test by means of the second equation. The further connection between  $\gamma$  and concentration is suggested by equation 16. If we assume an equilibrium between long and short range pairs, controlled by the balance between Coulomb forces and thermal motion, then we have the mass action equation

$$c\gamma^2 f^2 / (1 - \gamma) = K \quad (26)$$

where  $K^{-1}$  is given by equation 16. The term  $f^2$  is included in equation 26 to account for the effect of long range free ion-free ion interaction on the thermodynamic potentials involved in the derivation of equation 26. Following Debye and Hückel, we may set

$$-\ln f^2 = 2\beta' \sqrt{c\gamma} \quad (27)$$

because free ions, defined as those for most of which  $r \gg d$ , satisfy the Debye-Hückel approximation

$$\epsilon\psi/kT \ll 1 \quad (28)$$

necessary for the simplification of the Poisson-Boltzmann equation to a linear differential equation, and equation 27 is the direct result of this step.

Equations 21, 26, and 27 together then give conductance as a function of



concentration, and aside from universal constants, two arbitrary constants,  $\Lambda_0$  and  $K$  appear. It should therefore be possible to rearrange the equations so that conductance data can be plotted in such a way that a straight line is obtained, provided all our assumptions are correct. This form is readily found; as a matter of fact, it is simply the function used by Kraus and Bray (20) twenty years ago, modified to take into account long range interionic effects. By rearrangement of the fundamental equations, we obtain

$$\frac{F}{\Lambda} = \frac{1}{K\Lambda_0^2} \frac{c\Lambda f^2}{F} + \frac{1}{\Lambda_0} \quad (29)$$

so that  $F/\Lambda$  plotted against  $c\Lambda f^2/F$  gives a straight line with slope  $1/K\Lambda_0^2$  and intercept  $1/\Lambda_0$ . In figure 2 are given some examples for salts in liquid ammonia (17) ( $D = 22$ ) at  $-33^\circ\text{C}$ ., and in figure 3 for salts in ethylene

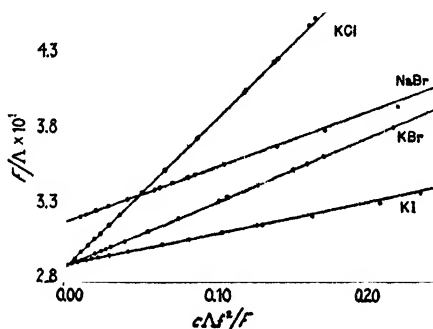


FIG. 2. Conductance function in liquid ammonia at  $-33^\circ\text{C}$ .

chloride (6) ( $D = 10.23$ ) at  $25^\circ\text{C}$ . Over a wide range of concentration, the plot is linear as required by equation 29.<sup>6</sup>

We may reverse the procedure and calculate the conductance curve, once values of the constants are obtained. In figure 4 are given calculated  $\Lambda - \sqrt{c}$  curves for a variety of conducting systems (12) covering a wide range of all the variables. The solid curves are calculated; the circles represent

<sup>6</sup> The procedure for making the plot, given experimental  $\Lambda - c$  values is as follows. First, a free-hand extrapolation of a  $\Lambda - \sqrt{c}$  curve or of a  $(\Lambda + \alpha\sqrt{c}) - c$  curve is made, in order to obtain a tentative value  $\Lambda'_0$  for the limiting conductance. Using this value,  $z$  is computed for each point, and the corresponding  $F$  is interpolated from the table (reference 6) or calculated by equation 24 or 25. Then  $\gamma$  is computed from equation 23, and with this value of  $\gamma$ , equation 27 is used to obtain  $f^2$ . Now both  $f^2$  and  $F$  will be somewhat in error if  $\Lambda'_0$  does not equal the true value of the limiting conductance, but these errors do not seriously affect the extrapolation for  $\Lambda_0$ . Then  $F/\Lambda$  is plotted against  $c\Lambda f^2/F$ , and the line constants are determined. If the value of  $\Lambda_0$  obtained from the intercept is more than a per cent or so different from  $\Lambda'_0$ , the calculation is repeated to obtain a second approximation, because the slope of the curve is affected by the  $\Lambda_0$  value used in the computation.

observed points. It should be noted that in principle two points are sufficient to determine the entire conductance curve, because only two arbitrary constants are involved. All the curves approach  $\Lambda_0$  along the Onsager tangent; in solvents of higher dielectric constant, the deviation from the limiting law

$$\Lambda = \Lambda_0 - \alpha\sqrt{c} \quad (30)$$

is small at low but accessible concentrations, because  $\gamma$  is nearly unity. In solvents of dielectric constant less than about 30, an inflection point appears at a concentration

$$c_{inf} = 0.2165 K/f_{inf}^2 \quad (31)$$

near which the curve is, of course, approximately linear. It is the appearance of this inflection point which has led to the statement appearing

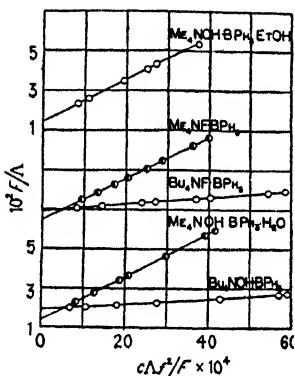


FIG. 3

FIG. 3. Conductance function in ethylene chloride at 25°C.

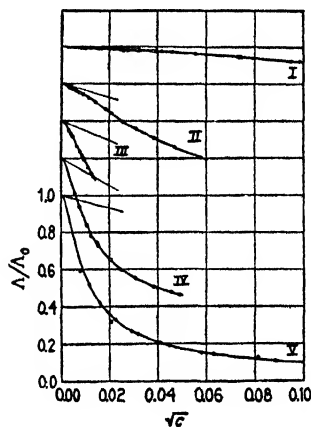


FIG. 4

FIG. 4. Calculated and observed conductance values. Curve I,  $\text{HIO}_3$  in water; curve II,  $\text{NaBrO}_3$  in ammonia; curve III,  $\text{NaI}$  in amyl alcohol; curve IV,  $(\text{C}_6\text{H}_{11})_4\text{N}\cdot\text{NO}_2$  in ethylene chloride; curve V,  $\text{KNH}_2$  in ammonia.

frequently in the literature that, in non-aqueous solvents, conductance curves approach linearity on a  $\sqrt{c}$  scale, but with a slope much greater than  $\alpha$ .

We must inquire how the constants  $\Lambda_0$  and  $K$  vary with more fundamental parameters. In first approximation,  $\Lambda_0$  depends primarily on the viscosity,  $\eta$ , of the solvent, as required by Walden's application of Stokes' law,

$$\Lambda_0\eta = \text{constant} \quad (32)$$

but it is probable that this product also depends on temperature, viscosity, and dipole moment of the solvent (4, 26). Also, in first approximation,

$K$  varies with ion size, dielectric constant, and temperature (13) in accordance with the following equation:

$$K^{-1} = \frac{4\pi L}{1000} \left( \frac{\epsilon^2}{DkT} \right)^3 [P(b) - P(\epsilon^2/DkTd)] \quad (33)$$

where

$$P(x) = Ei(x) - \frac{e^x}{x} \left( \frac{1}{x} + \frac{2}{x^2} + 1 \right) \quad (34)$$

For example, figure 5 shows the variation of the dissociation constant of tetraisoamylammonium nitrate in dioxane-water mixtures (21) over the

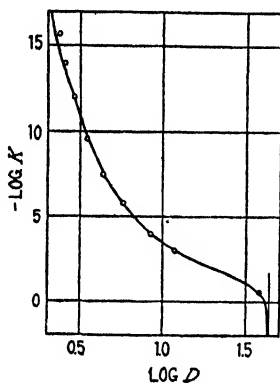


FIG. 5

FIG. 5. Calculated and observed dissociation constants for tetraisoamylammonium nitrate in dioxane-water mixtures.

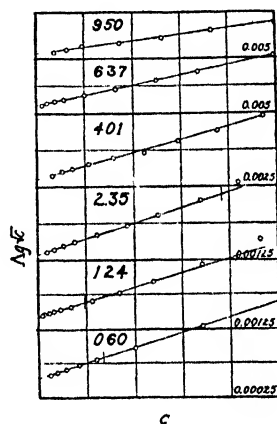


FIG. 6

FIG. 6. Test of the triple ion conductance function

range  $D = 2.38$  to  $D = 38$ . The circles are experimental values; the curve is calculated according to equation 33 with  $d = \beta/2$  and  $a = 6.40 \times 10^{-8}$  cm.

At low concentrations, therefore, we may, with a reasonable degree of certainty, describe and predict electrolytic properties. The next question deals, of course, with higher concentrations. It must be pointed out immediately that the meaning of the phrase "at low concentrations" depends on the solvent. For example, the behavior of 0.001  $N$  aqueous solutions is fairly well understood, but at the same concentration in benzene, electrolytic properties are far too complicated for analysis with any of our present methods.

The applicability of the hypothesis made above—namely, a combination of the effects of long range interionic forces with the effects due to ionic association—depends for its success, obviously enough, on the presence of free ions and associated pairs in the solution. Now as concentration is increased, we find a shift of the distribution curve  $G(r)$ , as is shown in figure 1, which eventually eliminates the long range maximum. At a concentration given by

$$c_{crit} = 3.2 \times 10^{-7} D^3 \text{ at } 25^\circ\text{C}. \quad (35)$$

the maximum of  $G(r)$ , the minimum and the included inflection point coincide. Above this concentration, there is no relative maximum probability for the free ions; the shorter the pairwise distances, the greater the probability. As a matter of fact, the simple conductance equation (equation 21) is found to fail at concentrations of the order of that given in equation 35; at higher concentrations,  $\Lambda$  (observed) is always greater than  $\Lambda$  calculated from equation 21. Frequently the observed curves show a minimum in conductance, beyond which  $\Lambda$  increases with  $c$ , while equation 21 calls for a decrease of  $\Lambda$  with increasing  $c$  as long as the equation has any physical meaning (i.e., as long as  $3\sqrt{3}z/2 \leq 1$ ).

It is therefore necessary to find some additional process which is taking place in the solution, in order to account for the positive deviations from equation 21. A suggestion regarding this is found in the restrictions involved in deriving the distribution function. We assumed that  $V$  was so large that short range three-ion configurations were negligibly rare, so that no  $1/r^2$  terms in ionic energies would be comparable with the  $1/r$  terms. At concentrations greater than that given in equation 35, many ions will be near short range pairs, because the distribution curve calls for a large fraction of the solute existing as short range pairs (cf. figure 1). The potential energy of a single ion in contact with an ion pair is, in the ideal case, one half the potential energy of the ion pair, and may therefore also be large compared to  $kT$ . Consequently, short range three-ion configurations will be stable to thermal impact, and we must re-define the distribution, in order to take these groups into account. Let us define a free ion as one which is relatively far from either another free ion or from a short range ion pair. Then, by an analysis entirely analogous to the one which led to  $G(r)$ , we find that short range triple ion groups have a relative maximum in probability when the dielectric constant becomes small or the concentration large. Furthermore, if we consider part of the solute to exist as triple ions, we are removing a part of the solute from the ion-ion equilibrium (17), and the net result is to remove some area from the  $G(r)$  curve near  $r = \beta/2$ , which restores the long range maximum. We now have five individual species of solute particles: (+), (−), (+ −), (+ − +), and (− + −).

It is easy to compute the effect of the presence of triple ions on the conductance (14). These groups have a net charge of  $\pm e$  and hence are conducting. Also the equilibrium between triple ions, ion pairs, and free ions obeys the formal laws of dissociation theory; the proof is analogous to that leading to equation 16. If, for the sake of simplicity, we assume that  $(+ - +)$  and  $(- + -)$  groups are equally probable,<sup>7</sup> we find the conductance equation

$$\Lambda \sqrt{c} g(c) = \Lambda_0 \sqrt{K} + \frac{\lambda_0 \sqrt{K}}{k_3} \left(1 - \frac{\Lambda}{\Lambda_0}\right), \quad (36)$$

Here  $\lambda_0$  is the limiting conductance of the hypothetical salt  $(+ - +)$   $(- + -)$ . The function (14)  $g(c)$  approximates the long range interionic effects; in it, total ion concentration is set equal to  $c\Lambda/\Lambda_0$  and cross terms in the mobility correction, caused by the difference between  $\Lambda_0$  and  $\lambda_0$ , are neglected (25). According to equation 36, we should obtain a straight line when  $\Lambda\sqrt{c}g(c)$  is plotted against  $c(1 - \Lambda/\Lambda_0)$ . In figure 6 are shown the corresponding curves for tetraisoamylammonium nitrate in dioxane-water mixtures (14) over the appropriate ranges of concentration. It will be seen that all the plots are linear. The line constants evaluate  $\Lambda_0\sqrt{K}$  and  $\lambda_0\sqrt{K}/k_3$  as intercept and slope. Now the triple ion hypothesis brings in three new arbitrary constants. By assuming  $(- + -)$  and  $(+ - +)$  groups equally probable, we reduce the number to two,  $\lambda_0$  and  $k_3$ . We may estimate  $\lambda_0$ , and thus determine  $k_3$ , or else make conductance measurements at at least two temperatures, which will then determine the two constants (2).

In the same way that  $K$  was expressed as a function of  $D$ ,  $T$ , and  $a$ , we find for  $k_3$

$$k_3^{-1} = \frac{2\pi\beta a^3}{1000} I(b) \quad (37)$$

The function  $I(b)$  has been tabulated for a series of  $b$ -values. When the parameter  $b$  is large compared to unity, we may use the asymptotic expansion (10).

$$I(b) \sim 32e^{b/2}/3b^2 \quad (38)$$

Equation 37 may be tested by plotting observed values of  $\log k_3$  against  $D$  and comparing with a  $\log k_3$ - $D$  curve calculated from equation 37, using a fixed  $a$ -value. In figure 7, we have such a plot for the data of figure 6,

<sup>7</sup> An inequality in probability causes a shift of the minimum to higher concentrations, other variables remaining constant. In the limiting case where one triple species does not form at all, the conductance curve approaches asymptotically a constant value, provided higher association does not produce a minimum.

with  $a = 9.0 \times 10^{-8}$  cm. The agreement is satisfactory over a wide range of the variables.

The development sketched above serves to account quantitatively for conductance curves up to concentrations of the order of that corresponding to the minimum in conductance, when a minimum appears, i.e., in solvents of dielectric constant less than about 10. For solvents of higher dielectric constant, triple ion energies are fairly small, and this type of interaction<sup>8</sup> cannot be treated by association theory, just as short range pairwise interaction cannot be so treated for strong electrolytes in solvents of high dielectric constant; and for the same reason, the energy is only of the same order as  $kT$ . The general problem of concentrated solutions of electrolytes is as yet practically untouched.

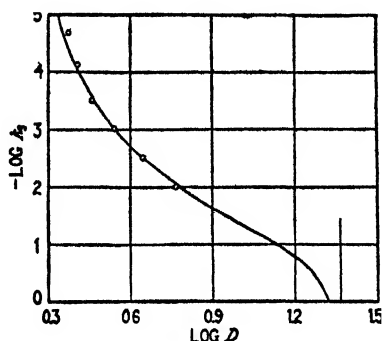


FIG. 7. Calculated and observed triple ion dissociation constants

In solvents of very low dielectric constant, association increases very rapidly with increasing concentration, if we base our opinion on molecular weight (1, 23) and dielectric constant measurements (22). The next simplest association after the triple ion is the quadrupole type, and it is possible to set up a system of equations which describes the limiting behavior of a pair-pair association in solvents of low dielectric constant (9). The agreement between theory and experiment is fairly satisfactory (16), but not many data are yet available and the theory is still in the process of development. The greatest practical difficulty in the treatment of even moderately concentrated electrolytic solutions in solvents of low dielectric constant lies in the fact that, with increasing order of association, the excess potential energy of the last ion added to a cluster becomes less and less. Consequently, the binding energy decreases with increasing

<sup>8</sup> The three-ion interaction in solvents of higher dielectric constant could probably be handled best by starting with the equations of motion (Fuoss: *Physik. Z.* **35**, 59 (1934)).

order of association, and, furthermore, it becomes difficult to separate individual orders, because their relative energies, and hence probabilities, are nearly equal. We can only draw the conclusion that association will increase very rapidly once the triple ion stage is passed; this conclusion is confirmed by experimental data on conductance (15), freezing points (1, 23), and dielectric constant (22). It is, however, quite possible that the conductance mechanism in concentrated solutions in solvents of low dielectric constant is different from the simple migration type characteristic for low concentrations, and an exchange of ions between neighboring clusters, corresponding to a rapid increase of effective mobility with increasing concentration, might easily be involved. Again we are faced with a lack of experimental data on which to base deductions. It is interesting to note that the high concentration ends of conductance curves for a given salt in solvents of low dielectric constant all tend to converge to the same region, which is presumably the conductance of the fused salt at the experimental temperature. This fact suggests that the best approach to the problem might be through the theory of the conductance in fused salts, another field which has been investigated in only a preliminary way.

## REFERENCES

- (1) BATSON AND KRAUS: *J. Am. Chem. Soc.* **56**, 2017 (1934).
- (2) BIEN, KRAUS, AND FUOSS: *J. Am. Chem. Soc.* **56**, 1860 (1934).
- (3) BJERRUM: *Kgl. Danske Videnskab. Selskab* **7**, No. 9 (1926).
- (4) BORN: *Z. Physik* **1**, 221 (1920).
- (5) DEBYE AND HÜCKEL: *Physik. Z.* **24**, 185, 305 (1923).
- (6) FOWLER, D. L., JR.: Thesis, Brown University, 1935.
- (7) FUOSS: *Trans. Faraday Soc.* **30**, 967 (1934).
- (8) FUOSS: *J. Chem. Physics* **2**, 818 (1934).
- (9) FUOSS: *J. Am. Chem. Soc.* **56**, 1027, 1031 (1934).
- (10) FUOSS: *J. Am. Chem. Soc.* **56**, 1857 (1934).
- (11) FUOSS: *J. Am. Chem. Soc.* **57**, 488 (1935).
- (12) FUOSS AND KRAUS: *J. Am. Chem. Soc.* **55**, 476 (1933).
- (13) FUOSS AND KRAUS: *J. Am. Chem. Soc.* **55**, 1019 (1933).
- (14) FUOSS AND KRAUS: *J. Am. Chem. Soc.* **55**, 2387 (1933).
- (15) FUOSS AND KRAUS: *J. Am. Chem. Soc.* **55**, 3614 (1933).
- (16) FUOSS AND KRAUS: *J. Am. Chem. Soc.* **57**, 1 (1935).
- (17) HNIZDA, VINCENT F.: Thesis, Brown University, 1935.
- (18) KIRKWOOD: *J. Chem. Physics* **2**, 351 (1934).
- (19) KIRKWOOD: *J. Chem. Physics* **2**, 767 (1934).
- (20) KRAUS AND BRAY: *J. Am. Chem. Soc.* **35**, 1315 (1913).
- (21) KRAUS AND FUOSS: *J. Am. Chem. Soc.* **55**, 21 (1933).
- (22) KRAUS AND HOOPER: *J. Am. Chem. Soc.* **56**, 2265 (1934).
- (23) KRAUS AND VINGEE: *J. Am. Chem. Soc.* **56**, 511 (1934).
- (24) ONSAGER: *Physik. Z.* **27**, 388 (1926); **28**, 277 (1926).
- (25) ONSAGER AND FUOSS: *J. Phys. Chem.* **36**, 2689 (1932).
- (26) SCHMICK, H.: *Z. Physik* **24**, 56 (1924).

# A SYMPOSIUM ON THE KINETICS OF REACTION<sup>1</sup>

## INTRODUCTION TO THE SYMPOSIUM

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*Received June 6, 1935*

Fundamental physical chemistry in America has shared in the pioneering investigations which are even now being turned to practical advantage. America is responsible for the modern concepts of surface reactions, through the illuminating studies of Langmuir. From America, outwards, have spread the accepted concepts of the catalytic surface and the scientific interpretation of the industrially important phenomena of poisons and of promoters, and of the nature of gaseous activation at surfaces which is so important in technical catalysis. American physical chemistry has fertilized the field of chain reactions, which are fundamental in processes of deterioration and in the operation of the internal combustion engine. The physical chemistry of nitrocellulose, of cellulose esters, and of other plastics provided the basis for the technical development of nitrocellulose paints and enamels, and for improvements in the fields of photography, artificial fibers, and cellophane. Abundant evidence of a dispassionate nature from foreign lands testifies to the fact that the high standards of American chemical science rest to a large extent on the excellence of its fundamental research in physical chemistry rather than on its contributions to other branches of the subject. It is a matter for meditation and discussion whether the American chemical industry has utilized to the fullest possible extent this abundance of excellent physical chemical material.

The effect of earlier discoveries on subsequent technical development should therefore stimulate our interest in the symposium which we hold

<sup>1</sup> The papers included under this title form part of an all-day symposium on "Kinetics of Reaction," which was presented by the Division of Physical and Inorganic Chemistry at the Eighty-ninth Meeting of the American Chemical Society in New York City on April 22, 1935. The morning session, which included the papers by H. S. Taylor, G. B. Kistiakowsky, F. O. Rice, V. K. La Mer and H. Eyring, was arranged by H. S. Taylor, and the introduction refers specifically to that session. The afternoon session, which included the papers by F. Daniels, H. A. Liebhafsky, W. F. K. Wynne-Jones, and L. P. Hammett, was arranged by L. P. Hammett.



today. We shall learn this morning of those newest studies in the field of reaction mechanism and reaction kinetics that are now issuing from prominent centers of our physical chemical science. They comprise, we believe, the beginnings of new and significant chapters in their special field, of decisive implications for applied science. In the review of new work in the field of thermal decomposition we shall learn of the important developments now taking place through the investigations of Professor Rice of Johns Hopkins University and those from the Harvard University Laboratories which Professor Kistiakowsky will report. These studies will serve to emphasize the importance of molecular fragments, atoms or free radicals, in many forms of chemical reactions. They have opened up an entirely new field of study of reactions hitherto thought to be simple unimolecular reactions. Much of the early work in this field will now, of necessity, be reexamined and reinterpreted in the light of concepts developed by Rice. It would be superfluous to emphasize the fundamental significance of these studies in the technically important pyrolytic reactions and explosion reactions. The fundamental studies have, at once, a technical implication.

In addition, however, we shall hear of the limitations of the present theoretical treatment of chemical kinetics. Professor La Mer will present experimental evidence of the inadequacy of current concepts in interpreting already available experimental material, especially in the realm of reaction velocities in solution. It will be shown that many reactions proceed at speeds which differ greatly from those calculable on the basis of simple collision theories, the efficiency of which collisions is governed by an exponential factor expressive of the energy of the fruitful collisions. It will be shown that rates of reaction varying a millionfold from normal expectation are not uncommon. The causes of such deviations will be presented by Professor Eyring. It will be shown that the technique of reaction rate measurements has been refined to a point where the classical theories of reaction kinetics are no longer adequate. Classical kinetics is based on a collisional mechanism, the molecules of which collisions have been assigned a nineteenth-century billiard-ball immutable structure. The wave-mechanical concepts of atomic structure have provided a more intimate picture. With their aid we can not only deduce the most favorable configurations of atomic or molecular approach but can interpret such approach in terms of the individual translational, rotational, and vibrational energies of the impinging molecules. With the aid of the quantum mechanics, for simple processes, the conversion of the kinetic energy of approach into the potential energy of the collisional system as a whole can already be charted on a contour map, from which the easiest path to reaction can be deduced with the facility with which the aviator can choose his airway through a mountain range with the more familiar geographical charts and maps of

the regions which he traverses. The new methods provide a more intimate interpretation of the activated complex, the intermediate high energy stage in the process of reaction, and with the aid of statistical mechanics, it is now possible, as Professor Eyring will show, not only to deduce theoretically all the results of the classical kinetics, but also to indicate in what directions our previous knowledge fails and how the newer concepts provide a satisfactory interpretation of the deviations found. The work is specialized. It is a beginning in the application of the newer pictures of the atom and the molecule to the central problem of the chemist,—reaction speed and reaction mechanism.

It is for such reasons that the Division of Physical and Inorganic Chemistry proudly sponsors its symposium on this anniversary occasion. Our service to the chemistry of the future, fundamental and industrial, is to provide a finer structure of chemical theory than has hitherto obtained. We are confident that, in our efforts to provide our science with a more comprehensive theoretical basis for the mechanics of reaction, we lay the foundations for a more skillful achievement of all reactions, in laboratory or factory. The years ahead will yield rich store of chemical progress. The present achievements of synthetic organic chemistry are but a faint indication of the syntheses which yet shall be achieved. We will play our part also in such developments. The synthetic reactions of the laboratory are, in comparison with processes *in vivo*, labored and inefficient. Progress towards the goal set by vital processes in the simplicity and ease of synthesis, metathesis, and decomposition is something to which we will contribute by our more penetrating analyses. For us to scale successfully the less accessible heights, our charts of reaction path will become ever more indispensable.



## GASEOUS UNIMOLECULAR REACTIONS

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It is now universally recognized that the source of activation of molecules in thermal unimolecular reactions is their collisions, and not the absorption of radiation as had been frequently proposed in the past. Lindemann (14), more than ten years ago advanced a plausible explanation of how the rate of this type of reaction can be of the first order despite the fact that the process is inherently due to molecular collisions, the frequency of which is proportional to the square of the gas pressure. He assumed that reaction follows activation with some delay, and that in the meantime the activated molecules—which are none other than the energy-rich molecules of the Maxwell-Boltzmann distribution—can lose their energy on other collisions. Clearly, so long as the activation and deactivation rates are much faster than reaction, the number of activated molecules will be the equilibrium number, that is, a constant fraction of the total number.

Since, furthermore, the reaction is supposed to take place spontaneously, in a manner similar to radioactive decompositions, a constant fraction of activated molecules will react and an overall first-order rate will result. As the pressure of the reactant gas is lowered more and more, the rates of activation and deactivation decrease proportionally to the number of molecular collisions, thus as the square of the pressure. The reaction then consumes an ever greater fraction of activated molecules, depressing their concentration below the equilibrium value and consequently lowering the reaction rate below the value predicted from the first-order rate equation. Finally, when on further lowering of the pressure the average time between activating and deactivating collisions has become much longer than the average time between activation and reaction, essentially all activated molecules undergo reaction and the reaction rate becomes equal to the rate of activation, that is, becomes of the second order.

In the years following Lindemann's suggestion his theory was not generally accepted, mainly because the rate of the then well-studied nitrogen pentoxide decomposition remained of the first order down to such low pressures (1 mm. and below) that the rate of activating molecular collisions seemed to be inadequate to explain the maintenance of the equilibrium

concentration of activated molecules. This difficulty was removed by Hinshelwood (7) and Lindemann, who pointed out that very much faster rates of activation result statistically if it is assumed that energy contained in several internal degrees of freedom of the molecule contributes to the activation. In earlier calculations, on the other hand, it was usually assumed that only one degree of freedom is involved in the process of activation. As the theory was being formulated, Hinshelwood succeeded in finding gaseous unimolecular reactions showing the desired falling-off of the first-order rate constant at lower pressures and thus a positive proof of the theory seemed to have been obtained. Considerable doubts exist at the present time concerning the real mechanism of reactions then studied by Hinshelwood, but other unimolecular reactions are known, owing chiefly to the work of Ramsperger, which are free from serious objections and which demonstrate the essential correctness of the Lindemann-Hinshelwood theory.

This theory received very essential improvement in the hands of O. K. Rice and Ramsperger (25) and of Kassel (8), who incorporated in it the idea that while energy contained in different parts of the molecule may contribute to activation, in order that reaction may occur a minimum energy of activation must become concentrated in the reacting part of the molecule. This concept leads to the idea that the greater the total amount of energy in a molecule, the greater is the chance that a given minimum amount (the "activation energy" of Arrhenius) will, as the result of statistical fluctuations, concentrate in a given bond of the molecule. Accordingly, activated molecules must have different reactivities; in other words, the average times between activation and reaction must be different for molecules with different amounts of energy in excess of the minimum required amount. These improvements change somewhat the quantitative dependence of the rate on pressure and temperature, but leave the essential features of the original theory intact. In those few cases where the dependence of the rate on pressure has been accurately studied, a quantitative agreement with the Rice-Kassel theories has been obtained.

Quite naturally, the development of a satisfactory theory was followed by active experimental work, and in recent years quite a number of gaseous decompositions involving large molecules have been interpreted as of unimolecular type. It is indeed quite probable that unimolecular processes play an important part in these reactions; but on the other hand, owing to a great extent to the work of F. O. Rice, it is being recognized now that in many such reactions—particularly those occurring at higher temperatures—secondary processes are quite complex, completely obscuring the kinetics of the primary step and leading to the establishment of reaction chains. As has been shown by Rice and Herzfeld (23), such reaction chains in

organic decompositions can readily lead to kinetic expressions superficially similar to those of unimolecular reactions. It is therefore necessary to

TABLE 1  
Some unimolecular reactions.  $k = Ae^{-\frac{E}{RT}} \text{ sec.}^{-1}$

REACTING SUBSTANCE	REFERENCE	E	A	NUMBER OF CLASSICAL OSCILLATORS PARTICIPATING IN ACTIVATION
Decomposition reactions				
N <sub>2</sub> O.....	(15)	53,000	$4.2 \times 10^9$	1
F <sub>2</sub> O.....	(11)	39,000	$> 10^{12}$	3
N <sub>2</sub> O <sub>4</sub> .....	(26)	13,900	$8.0 \times 10^{14}$	10 ?
N <sub>2</sub> O <sub>5</sub> .....	(6)	24,590	$3.8 \times 10^{12}$	15 ?
ClCOOCCl <sub>3</sub> .....	(22)	41,500	$1.4 \times 10^{13}$	7
CH <sub>3</sub> N <sub>3</sub> .....	(12)	43,500	$3.0 \times 10^{15}$	13
C <sub>2</sub> H <sub>5</sub> N <sub>3</sub> .....	(13)	39,700	$2.0 \times 10^{14}$	14
CH <sub>3</sub> NNCH <sub>3</sub> .....	(18)	52,400	$3.1 \times 10^{15}$	12
CH <sub>3</sub> NNC <sub>2</sub> H <sub>5</sub> .....	(20)	47,500	$2.8 \times 10^{15}$	16
C <sub>2</sub> H <sub>7</sub> NNC <sub>2</sub> H <sub>5</sub> .....	(19)	40,900	$5.7 \times 10^{13}$	>25
CH <sub>3</sub> N <sub>2</sub> HCH <sub>3</sub> .....	(21)	33,800	$4.0 \times 10^{11}$	7
CH <sub>3</sub> I.....	(17)	43,000	$3.9 \times 10^{12}$	7
C <sub>2</sub> H <sub>5</sub> I.....	(17)	43,000	$1.8 \times 10^{13}$	9
C <sub>2</sub> H <sub>7</sub> I.....	(17)	43,000	$2.8 \times 10^{13}$	>10
CH <sub>3</sub> NO <sub>2</sub> .....	(28)	36,400	$9.0 \times 10^{12}$	>12
C <sub>2</sub> H <sub>5</sub> NO <sub>2</sub> .....	(28)	37,700	$7.0 \times 10^{13}$	>12
CH <sub>3</sub> CH(OOCCCH <sub>3</sub> ) <sub>2</sub> .....	(2)	32,900	$2.0 \times 10^{10}$	?
CH <sub>3</sub> CH(OOCC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> .....	(3)	32,900	$2.5 \times 10^{10}$	?
C <sub>2</sub> H <sub>7</sub> CH(OOCCCH <sub>3</sub> ) <sub>2</sub> .....	(3)	32,900	$3.2 \times 10^{10}$	?
(CH <sub>3</sub> ) <sub>3</sub> COH.....	(27)	65,500	$4.8 \times 10^{14}$	19
(CH <sub>3</sub> ) <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )COH.....	(27)	60,000	$3.3 \times 10^{12}$	?
(C <sub>2</sub> H <sub>5</sub> O) <sub>2</sub> .....	(4)	44,200	$1.3 \times 10^{15}$	?
(n-C <sub>4</sub> H <sub>9</sub> O) <sub>2</sub> .....	(5)	42,000	$2.4 \times 10^{14}$	?
(iso-C <sub>4</sub> H <sub>9</sub> O) <sub>2</sub> .....	(5)	42,000	$2.8 \times 10^{14}$	?
Isomerizations				
Cyclopropane.....	(1)	65,000	$1.5 \times 10^{15}$	12
2-Methyl maleic ester.....	(16)	26,500	$6.8 \times 10^5$	<1
cis-Methyl cinnamic ester.....	(10)	41,600	$3.5 \times 10^{10}$	6
cis-Stilbene.....	(9)	42,800	$6.0 \times 10^{12}$	>12
Pinene.....	(29)	43,700	$1.3 \times 10^{14}$	?

exercise some caution in selecting from the list of known reactions those which should be used as examples of unimolecular processes. Table 1 represents one such selection.

The table is subdivided into two parts: decomposition and isomerization reactions. The first column gives the reacting substance, but for the sake of brevity the reaction products have not been included. In many instances they are more complex than would be strictly desirable from the point of view of the unimolecular mechanism, and it is necessary occasionally to assume that the primary unimolecular decomposition is followed by several secondary reactions, which are, however, of such a type as not to obscure the kinetics of the primary step.

The second column gives the activation energies of the reactions calculated from the temperature coefficients of the rate. It will be observed that in several instances these energies are considerably smaller than those usually associated with the strength of bonds supposed to be broken in the reactions, but this is not necessarily a severe criticism of the unimolecular mechanism. Thus, from photochemical work it is well known that in some processes of decomposition the fragments of the original molecule rearrange into more stable configurations, the energy thus set free being utilized in the process of severing the bonds.

A few of the reactions in the table have been studied with several homologues, and the general rule seems to be that the energy of activation remains essentially constant in each case. Exceptions to this have been observed with azides, azo compounds, and tertiary alcohols, and with *cis-trans* isomerizations. The first three reactions recently received a satisfactory explanation, in terms of the somewhat special properties of the methyl group, by Rice and Gershinowitz (24), while the last reaction is as yet not understood.

The next column gives the temperature independent factor of the first-order rate constant calculated for the limit of very high pressures of the reactant. In the theories of O. K. Rice and Ramsperger and of Kassel this factor,  $A$ , represents the intrinsic rate of reaction of activated molecules possessing a specified excess of energy over the necessary minimum, the rate being a prescribed, but an entirely reasonable, function of the excess energy. In the decomposition of  $F_2O$  it has not been possible to reach sufficiently high pressures to determine the limiting rate constant, and therefore only the lower limit of the constant  $A$  can be given; in the other reactions of table 1 the limiting rate has been almost realized experimentally.

The table shows quite considerable variations of the factor  $A$  from reaction to reaction and the older ideas that it could be set equal to  $10^{13}$  or connected to the activation energy by the relation

$$A = \frac{E}{hN_{Av}}$$

is seen to be only a rough approximation, although many reactions do possess  $A$  factors of this order of magnitude.

Some understanding of the causes of the wide variations of the  $A$  factor in many reactions has been gained recently by Rice and Gershinowitz (24). Upon considering the hypothetical equilibrium between the reactant molecule and its immediate decomposition products and the mechanism of the reverse (association) reaction, they conclude that when considerable "steric hindrance" or, to be more precise, a necessity for strict orientation exists in reforming the molecule from its products (as in the case of ethylidene diacetate and its homologues, for instance), the  $A$  factor of the forward reaction must be small and *vice versa*. Their calculations give very satisfactory agreement with experimental data and explain in particular why in a number of reactions involving the breaking-off of a methyl group, the  $A$  factor is so large; they suppose that in the instant of reaction a methyl group is capable of much freer motions in the molecule than a similar but larger group.

Connected with this is the larger activation energy usually observed with methyl compounds. This theory does not attempt to explain the exceptionally low  $A$  factors observed in a few reactions. That of the nitrous oxide decomposition, however, has been attributed to the occurrence of an electronic transition, an explanation strongly supported by the existing evidence. The isomerizations of maleic ester and of two other aliphatic double bond compounds (not given here), on the other hand, lack at present any satisfactory theory.

The last column of the table gives the number of vibrations in the molecule, supposed to have classical energy content for simplicity in treatment. This number must be assumed to contribute to the activation, if the pressure range where the falling-off of the rate constant has been found, is to be reconciled with the rate observed. The pressures at which falling-off becomes noticeable vary in different reactions from several atmospheres (nitrous oxide,  $F_2O$ , maleic ester) to pressures much lower than 1 mm. mercury (nitrogen pentoxide, azoisopropane, etc.). In the case of two molecules—nitrogen tetroxide and nitrogen pentoxide—the theory must be strained by assumption of large molecular diameters and excessive heat capacities if the observed rates are to be accounted for. In other cases the numbers found seem to be quite reasonable, and show in general the expected tendency to increase with increasing complexity of the molecule. However, too little is known on this subject to make possible extensive deductions.

Taken together, all these experimental observations leave no doubt that the present theories of unimolecular reactions are essentially correct and that they may need only minor improvements in the near future. Already,



they furnish us with considerable information concerning the mechanics of molecular processes and should, when more experimental material is available, be of considerable help in the general study of molecular properties.

## REFERENCES

- (1) CHAMBERS AND KISTIAKOWSKY: J. Am. Chem. Soc. **56**, 399 (1934).
- (2) COFFIN: Can. J. Research **5**, 636 (1931).
- (3) COFFIN: Can. J. Research **6**, 417 (1932).
- (4) COFFIN: Can. J. Research **7**, 75 (1932).
- (5) COFFIN: Can. J. Research **9**, 603 (1933).
- (6) DANIELS AND JOHNSTON: J. Am. Chem. Soc. **43**, 53 (1921).
- (7) HINSHELWOOD: Proc. Roy. Soc. London **113A**, 230 (1926).
- (8) KASSEL: J. Phys. Chem. **32**, 225 (1928).
- (9) KISTIAKOWSKY AND SMITH: J. Am. Chem. Soc. **56**, 638 (1934).
- (10) KISTIAKOWSKY AND SMITH: J. Am. Chem. Soc. **57**, 269 (1935).
- (11) KOBLITZ AND SCHUMACHER: Z. physik. Chem. **25B**, 283 (1934).
- (12) LEERMAKERS: J. Am. Chem. Soc. **55**, 2719 (1933).
- (13) LEERMAKERS: J. Am. Chem. Soc. **55**, 3098 (1933).
- (14) LINDEMANN: Trans. Faraday Soc. **17**, 598 (1922).
- (15) NAGASAKO AND VOLMER: Z. physik. Chem. **10B**, 414 (1930).
- (16) NELLES AND KISTIAKOWSKY: J. Am. Chem. Soc. **54**, 2208 (1932).
- (17) OGG: J. Am. Chem. Soc. **56**, 526 (1934).
- (18) RAMSPERGER: J. Am. Chem. Soc. **49**, 1495 (1927).
- (19) RAMSPERGER: J. Am. Chem. Soc. **50**, 714 (1928).
- (20) RAMSPERGER: J. Am. Chem. Soc. **51**, 2134 (1929).
- (21) RAMSPERGER AND LEERMAKERS: J. Am. Chem. Soc. **53**, 2061 (1931).
- (22) RAMSPERGER AND WADDINGTON: J. Am. Chem. Soc. **55**, 214 (1933).
- (23) RICE, F. O., AND HERZFELD: J. Am. Chem. Soc. **56**, 284 (1934).
- (24) RICE, O. K., AND GERSHINOWITZ: J. Chem. Physics. In press.
- (25) RICE, O. K., AND RAMSPERGER: J. Am. Chem. Soc. **50**, 617 (1928).
- (26) RICHARDS AND REID: J. Chem. Physics **1**, 114 (1933).
- (27) SCHULTZ AND KISTIAKOWSKY: J. Am. Chem. Soc. **56**, 395 (1934).
- (28) STEACIE AND SHAW: J. Chem. Physics **2**, 345 (1934).
- (29) THURBER AND JOHNSON: J. Am. Chem. Soc. **52**, 786 (1930).

# THE DECOMPOSITION OF ORGANIC COMPOUNDS FROM THE STANDPOINT OF FREE RADICALS

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The changes which organic substances undergo when the temperature is raised have been made the subject of a great number of studies, especially during the past fifty years (10). The earlier work consisted of passing the substance to be investigated through a hot tube under conditions which brought about complete or almost complete decomposition of the original substrate. The permanent gases formed were analyzed in a gas analysis apparatus and the liquids were separated and identified by distillation. Unfortunately the immense number of data obtained in this way do not give us any appreciable understanding of the pyrolytic process. Except in the case of the very simplest substrate molecules, the products of the primary decomposition themselves decompose until finally secondary reactions predominate. This difficulty has been overcome in recent years by plotting the analysis of the products (15, 16, 34) against percentage decomposition of the original substrate; extrapolation of the curves to zero decomposition indicates the primary products of the decomposition and their relative amounts. Work of this nature has given information regarding the primary products of decomposition of certain hydrocarbons (5) and of acetone (24). However the information regarding primary products is still very meager and is not at all certain even in the case of substances such as diethyl ether, on which a large number of kinetic studies have been made (33). Further experimental work on the primary products formed in the thermal decomposition of one or two members of such series as ethers, ketones, esters, and amines is very desirable.

The existence of such a large number of empirical experimental data in this field constitutes a challenge to any chemist interested in the understanding of the mechanism of chemical reactions. In the last ten years much work has been done in investigating organic decompositions from the physical chemical standpoint. The chief pioneer in this field was Hinshelwood (6), who showed that the thermal decompositions of a number of simple organic molecules such as acetone (8) and dimethyl ether (7) are homogeneous and at sufficiently high pressures follow a unimolecular law.

The interpretation given to these experimental results (6) was that each organic molecule, depending on its energy content, has a certain probability of decomposing either directly into product molecules or at most through one or two intermediate steps. By assuming that activated molecules have a finite life and that their rate of production (except at fairly low pressures) is high compared with their rate of destruction chemically, it is possible to account for the experimental results. Indeed the development of this concept (6), especially by Hinshelwood, O. K. Rice, and Kassel, gave an apparently satisfying picture of those organic thermal decompositions which follow a unimolecular law.

There were, however, certain difficulties connected with the development of this picture. In part these were due to the inadequacy of the chemical analytical work necessary to supplement the kinetic measurements. For example, in the case of acetone we know now that the original conclusions of Hinshelwood and Hutchinson (8) regarding the chemical decomposition of acetone were incorrect (31), and in other cases, such as that of diethyl ether, the chemical data available are not yet complete in so far as the primary products of the reaction are concerned. A further difficulty arose when it was discovered (12) that acetaldehyde did not decompose according to a simple bimolecular law as originally reported, but that its decomposition could be best represented as of some fractional order (25), possibly 1.5. However it is possible that these various difficulties can be satisfactorily met; furthermore, the idea that product molecules result directly may be finally proved experimentally and the picture can then be extended to cover the calculation of the product molecules in some such way as suggested by Kassel (13).

About six years ago it occurred to the author (21) that the products of organic decompositions could be satisfactorily explained by assuming a primary decomposition into free radicals followed by a free radical chain which finally terminates by collision of the radicals. The scheme was relatively free from arbitrary assumptions and a detailed examination showed that on the basis of the available evidence it could account both qualitatively and quantitatively for the chemical products formed in organic decompositions (22). At about the time this idea was conceived, Paneth's discovery (17) of the free methyl radical was published. Experimental tests were then made with many organic compounds (27), using Paneth's technic, and it was shown that dissociation into free radicals could be experimentally demonstrated. The activation energies of these free radical dissociations were also measured (26) and shown to be not much higher than the overall decompositions. Certain free radicals were prepared (4) and their decomposition and interaction were found to be in excellent agreement with the free radical theory. Furthermore it was found that

the introduction of free radicals, produced either thermally (1, 36) or photochemically (14), induced extensive decomposition in butane, acetaldehyde, and dimethyl ether. Finally it was shown that the observed kinetics of the decompositions of ethane, dimethyl ether, acetone, and acetaldehyde could be satisfactorily explained on the basis of the free radical mechanism (25).

At present the situation is that both mechanisms are in fairly satisfactory agreement with experimental studies of the kinetics of organic decompositions. Indeed it is possible that the process involving the direct formation of product molecules and that involving a chain reaction may each occur to an appreciable extent for many organic reactions. Many experiments have been made in this laboratory to find an inhibitor which would remove free radicals and thus slow up any chain reaction that might be occurring; this work is still in progress and has shown that organic nitrites probably can act as chain breakers under certain conditions (29).

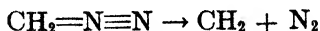
It may be pointed out that the adoption of the free radical mechanism for the bulk of organic thermal decompositions, while it would complicate the kinetic picture considerably, would not affect the theoretical development (6) of Hinshelwood, O. K. Rice, and Kassel, which would apply to the primary rupture into free radicals. On the other hand the adoption of the free radical mechanism would bring a great simplification into the organic chemistry of thermal decompositions (28): a few hundred elementary reactions describing the dissociation of organic molecules into radicals and the decomposition and reactions of these radicals would suffice to describe completely many thousands of organic decompositions. Possibly the future of this branch of organic chemistry may lie in the determination of the activation energies of organic reactions.

#### REACTION KINETICS

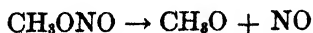
The detailed treatment (25) of the kinetics of organic decompositions from the free radical standpoint has already been given and will not therefore be repeated here. Since, however, the detailed treatment is necessarily very complicated, it seems desirable to present an artificially simplified scheme which contains all the important reactions. The primary reaction may consist of a dissociation into a smaller molecule and a radical,



Examples of such primary dissociations are the dissociation of diazomethane,



or of methyl nitrite (37, 38),



In other cases the primary dissociation may produce two radicals which may be like as in ethane or unlike as in acetone. These would be represented by the general equations  $M_1 \rightarrow 2R$  or  $M_1 \rightarrow R_1 + R_2$ . A radical produced in the primary dissociation may decompose into a smaller radical and a molecule or may react with one of the original substrate molecules by removing a hydrogen atom to form the radical hydride and a large free radical, which in turn decomposes to give a smaller radical and a molecule. The simplest form of this radical chain decomposition may be represented by the equations:



where the  $M$ 's represent molecules and the  $R$ 's represent radicals. The kinetics of the decomposition are not affected, except for a small factor in the chain length, if  $M_1$  decomposes into two radicals or if the radical  $R_1$  decomposes before reacting or if the chain radical is not the same as the radical produced in the primary dissociation.

Since the primary reaction (1) involves the dissociation of a molecule and consequent rupture of a bond, the activation energy should be high, and for those processes involving rupture of a carbon-carbon or carbon-oxygen bond may be expected to be very approximately 80 Cal. On the other hand, reactions 2 and 3, since they involve radicals, would be expected to have relatively low energies of activation. The termination of the chain may occur by collision of the radicals according to one of the three equations,



Equation 6 can be omitted from consideration on the basis that the large molecule  $M_6$  is unstable and easily dissociates into  $R_2$ . Whether the chain terminates according to equation 4 or equation 5 will depend on the relative activation energies of the two chain reactions 2 and 3. Here two cases arise. In the first, we assign a low activation energy ( $\sim 15$  Cal.) to reaction 2 and a relatively high activation energy ( $\sim 40$  Cal.) to reaction 3. The effect of this, if the reaction occurs at approximately atmospheric pressure, is to keep the concentration of  $R_1$  very low and the concentration of  $R_2$  relatively high. The radical  $R_2$  cannot disappear by combination with itself according to equation 6, owing to the instability of  $M_6$ , and re-

combination of  $R_1$  according to reaction 5 is slow compared with reaction 4, owing to the low concentration of  $R_1$ ; consequently reaction 4 breaks the chain.

In the second case we assign the same activation energy ( $\sim 15$  Cal.) to reaction 2, but a low activation energy ( $\sim 10$  Cal.) to reaction 3. This makes the radical  $R_2$  so unstable that its concentration is very low and the chain terminates by reaction 5, in which  $R_1$  combines with itself. It is interesting to note that at low pressures the first case passes over to the second, because the bimolecular reaction 2 is slowed up by the diminution in pressure as compared with unimolecular reaction 3; the concentration of  $R_1$  therefore rises until finally reaction 5 predominates instead of reaction 4.

We shall discuss briefly the kinetics of the first case, in which reaction 4 is the chain-terminating reaction. In the early states of the reaction after a steady state has been reached the radicals  $R_1$  and  $R_2$  are produced and destroyed at equal rates and consequently their rate of change is zero. We have then:

$$\frac{dR_1}{dt} = 0 = k_1M_1 - k_2R_1M_1 + k_3R_2 - k_4R_1R_2$$

$$\frac{dR_2}{dt} = 0 = k_2R_1M_1 - k_3R_2 - k_4R_1R_2$$

By adding these two equations we obtain,

$$0 = k_1M_1 - 2k_4R_1R_2$$

We then make an approximation by assuming that the chain is fairly long, so that we can neglect  $k_1M_1$  and  $k_4R_1R_2$  in comparison with  $k_2R_1M_1$  and  $k_3R_2$  in the first equation. We then obtain,

$$0 = k_3R_2 - k_2R_1M_1$$

Solving this equation and the previous one gives:

$$R_1 = \sqrt{\frac{k_1k_3}{2k_2k_4}} \quad R_2 = M_1 \sqrt{\frac{k_1k_2}{2k_3k_4}}$$

The overall rate of decomposition of  $M_1$  is given by

$$\begin{aligned} -\frac{dM_1}{dt} &= k_1M_1 + k_2R_1M_1 = k_1M_1 \left( 1 + \frac{k_2}{k_1} \sqrt{\frac{k_1k_2}{2k_3k_4}} \right) \\ &= k_1M_1 \left( 1 + \sqrt{\frac{k_2k_3}{2k_1k_4}} \right) \\ &\sim M_1 \sqrt{\frac{k_1k_2k_3}{2k_4}} \end{aligned}$$

We have therefore the totally unexpected result that a highly complicated chain decomposition may yet follow a simple unimolecular law.

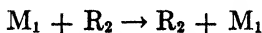
By following an exactly similar method for the case where the chain ends by reaction 5, we obtain

$$-\frac{dM_1}{dt} \sim M_1^{1.5} k_2 \sqrt{\frac{k_1}{k_5}}$$

The rate is therefore proportional to the 1.5 power of the concentration of the substrate molecule.

The schemes presented in this section of the paper would be expected to apply to organic molecules that contain only one kind of hydrogen atom, such as ethane, dimethyl ether, acetone, and neopentane; also it would be expected to apply to organic molecules which contain, owing to some peculiarity of structure, one kind of hydrogen atom which is much more loosely bound than any other kind. Acetaldehyde and pentene-1 are examples of such molecules.

On the other hand, when an organic molecule contains two or more kinds of hydrogen atoms, the problem becomes much more complicated. A preliminary study of this case has been made by Professor Herzfeld and the author, but it has been temporarily interrupted because of the lack of reliable data for the initial rates of decomposition of large molecules. From the radical standpoint we would expect the experimental result that two organic compounds when mixed do not decompose independently of each other, since the free radicals generated by the one affect the decomposition of the other and *vice versa*. This raises a difficulty in the experimental study of large molecules, because in many cases the product molecules contain hydrogen atoms much more loosely bound than the original substrate molecule; this would be expected to bring about a catalytic effect which would make the experimental determination of the initial rate of decomposition difficult. It is also very difficult to allow for this in the calculations, since the introduction of a catalyst by the reaction itself would not permit the assumption of a steady state concentration of the chain radicals. However, the calculations made so far have indicated that the methods used in previous papers for predicting the products of chemical decompositions are justified if a regeneration reaction of the type,

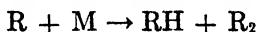


occurs in these chemical decompositions.  $R_2$  is simply a large radical formed by removal of a hydrogen atom from the original substrate molecule  $M_1$ , and the equation simply states that  $R_2$  is in general regenerated many times before it decomposes into a molecule and a smaller radical.

## FREE RADICAL CHEMISTRY

Only very few aliphatic free radicals have been isolated, namely methyl, ethyl, and methylene. In studying the radicals advantage is taken of their property, discovered by Paneth (17), of combining with certain metals. When free radicals are generated at low pressures (0.1 to 2 mm.) in a gas which is brought in contact with a cold metallic surface, the radicals diffuse to the surface and form a volatile organometallic compound. With few exceptions attempts to bring about reaction of radicals with solid surfaces other than metals and a few non-metallic elements results in recombination of the radicals with each other. Since the reaction  $R_1 + R_2$  may be expected to occur after relatively few collisions to yield the molecule  $R_1R_2$  (or two molecules) by disproportionation, it follows that the life of radicals will be very short. Actually it is found to be of the order of  $10^{-8}$  sec.

Attempts to make radicals react with organic molecules at surfaces have not been successful up to the present, but in the gas phase radicals have been shown to react very readily with many kinds of organic molecules such as ethylene (39, 40), acetaldehyde (1, 36), dimethyl and diethyl ethers (14), and acetone (30). These reactions are probably of the type



where the free radical  $R$  removes a hydrogen atom from the molecule  $M$  to form the molecule  $RH$  and the radical  $R_2$ , which is the original substrate minus a hydrogen atom. This type of reaction, which in general generates a new free radical at each elementary reaction, is most important from the organic chemical standpoint, since a chain reaction is thus propagated which determines the chemical products.

It seems desirable to list some of the different classes of free radicals and to comment briefly on their properties:

*Hydrocarbon radicals*

(a) *Univalent.* These may be considered to be derived from saturated hydrocarbons by removal of a hydrogen atom. The radicals from the paraffin series may be listed as follows:  $CH_3$ ,  $CH_3CH_2$ ,  $CH_3CHCH_3$ ,  $(CH_3)_3C$ ,  $CH_3CH_2CH_2$ ,  $CH_3CH_2CHCH_3$ ,  $CH_3CH_2CH_2CH_2$ , . . . . They have been placed in diminishing order of stability with reference to the reaction,

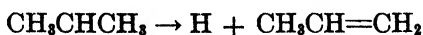
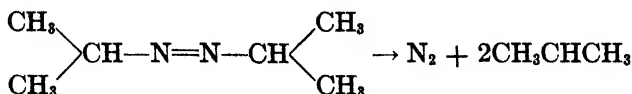


where  $M$  is a molecule or atom and  $R_1$  is a smaller radical than the original radical  $R$ . Of this series only  $CH_3$  and  $CH_3CH_2$  have been prepared (17, 18). Attempts to prepare  $CH_3CH_2CH_2$  and  $CH_3CH_2CHCH_3$  have so far been unsuccessful (18).



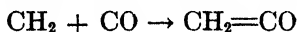
An attempt by the author<sup>1</sup> and A. T. W. Aten, Jr., to prepare the isopropyl radical by the decomposition of azoisopropane at low pressures was also unsuccessful, since only methyl groups were found.

From the following scheme

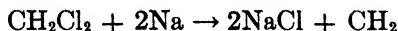


we may conclude that at low pressures the last reactions predominate, whereas at higher pressures recombination of the isopropyl radicals occurs (20). The important work of Frey on the decomposition of some mercury dialkyls (4) makes it highly probable that the *n*-butyl and *sec*-butyl radicals do have a real existence.

(b) *1,1-Bivalent*. Removal of two hydrogen atoms from the same carbon atom of an aliphatic hydrocarbon gives these radicals. Examples are:  $\text{CH}_2$ ,  $\text{CH}_3\text{CH}$ ,  $\text{CH}_3\text{CCH}_3$ . Several claims have been made that the methylene radical has been isolated. Staudinger and Kupfer (35) indicated its transitory existence by decomposing diazomethane in carbon monoxide and obtaining ketene. This was represented by the following equations:



Paneth has recently reported (19) that he was unable to isolate this radical by the reaction



whereas Belchetz (2) has reported its isolation by the thermal decomposition of methane. Rice and Glasebrook (23) reported the isolation of the methylene radical by decomposing diazomethane at low temperatures and passing the products over tellurium mirrors. At high temperatures the methylene radicals disappeared and were replaced by methyl groups. More recent work in this laboratory<sup>2</sup> has thrown doubt on Rice and Glasebrook's earlier work, since cold diazomethane vapor appears to react with the tellurium vapor over a hot tellurium mirror to form telluroformaldehyde. When experiments were performed under conditions such that this

<sup>1</sup> Unpublished work.

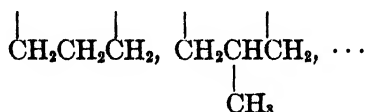
<sup>2</sup> Unpublished work by Rice and Bongiorno.

error was avoided, only methyl groups came out of the furnace. Thus even with pure diazomethane in pure nitrogen, methyl groups were obtained and carbon was deposited in the furnace. Similar experiments using methane or diethyl ether as carrier gas also yielded only methyl groups, so that it now appears that this radical is so exceedingly reactive that it will be very difficult to obtain it by the Paneth technic. It seems clear from attempts made to prepare the ethylidene radical that it has at best an exceedingly short life and isomerizes with great readiness to give ethylene. Probably all the 1,1-divalent radicals undergo this type of isomerization very easily.

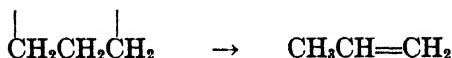
(c) *1,2-Bivalent*. These are the ethylene series of hydrocarbons. They do not show the reactions of free radicals towards metals, as might be expected if they existed in an "opened up" form (11):



(d) *1,3-Trivalent*. These may be represented by the formulas



The decomposition of cyclopropane<sup>3</sup> does not cause removal of metallic mirrors, from which it may be inferred that if this radical is formed at all, the isomerization,



occurs very easily; probably this is true also for its homologs.

(e) *1,4-Bivalent*. The simplest member of this series,  $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_2-$ , might be expected to be formed in the decomposition of cyclobutane. Possibly it isomerizes very easily to butene-2, or possibly it decomposes to ethylene. The decomposition of cyclobutane does not appear to have been studied experimentally.

(f) *Trivalent hydrocarbon radicals*. Nothing appears to be known chemically of the behavior of 1,1,1 radicals such as  $\text{CH}_3$ , or 1,1,2 radicals such as the vinyl radical,  $-\text{CH}_2-\text{CH}=\cdot$ . The trivalent radical,  $\text{CH}_2\text{CHCH}_2$ , and its homologs have been studied theoretically (28), and it has been found possible to give a satisfactory account of the thermal decompositions of the olefin hydrocarbons by assuming the intermediate formation of these radicals.

<sup>3</sup> Unpublished work by Rice and Glasebrook.

It may be of interest to list some of the various types of radicals that contain oxygen. These are formed by removal of a hydrogen atom from an alcohol, aldehyde, ether, ketone, etc.

<i>Oxo radical</i>	<i>Examples</i>
$R-O\cdot$	$CH_3O\cdot, CH_3CH_2O\cdot$
$\begin{array}{c}   \\ RCHOH\cdot \end{array}$	$CH_2OH\cdot, CH_3CHOH\cdot$
$\begin{array}{c}   \\ ROCH_2\cdot \end{array}$	$CH_3OCH_2\cdot, CH_3CH_2OCH_2\cdot$
$\begin{array}{c}   \\ ROCH_2CH_2\cdot \end{array}$	$CH_3OCH_2CH_2\cdot, CH_3CH_2OCH_2CH_2\cdot$
$\begin{array}{c}   \\ RC=O\cdot \end{array}$	$HCO\cdot, CH_3CO\cdot, CH_3CH_2CO\cdot$
$\begin{array}{c}   \\ RCHCHO\cdot \end{array}$	$CH_2CHO\cdot, CH_3CHCHO\cdot$

The isolation and study of these radicals is work that lies in the future. Possibly the solution of the problems of organic reactions lies in measurements of the activation energies of radical-molecule reactions and radical decompositions and interactions.

#### REFERENCES

- (1) ALLEN AND SICKMAN: J. Am. Chem. Soc. **56**, 2031 (1934).
- (2) BELCHETZ: Trans. Faraday Soc. **34**, 170 (1934).
- (3) FREY: Ind. Eng. Chem. **26**, 200 (1934).
- (4) FREY AND HEPP: J. Am. Chem. Soc. **55**, 3357 (1933).
- (5) FREY AND HEPP: Ind. Eng. Chem. **25**, 441 (1933).
- (6) HINSHELWOOD: Kinetics of Homogeneous Gas Reactions. Oxford University Press, London (1934).
- (7) HINSHELWOOD AND ASKEY: Proc. Roy. Soc. London **115A**, 215 (1927).
- (8) HINSHELWOOD AND HUTCHINSON: Proc. Roy. Soc. London **111A**, 245 (1926).
- (9) HINSHELWOOD AND HUTCHINSON: Proc. Roy. Soc. London **111A**, 380 (1926).
- (10) HURD: Pyrolysis of Organic Compounds. The Chemical Catalog Co., Inc., New York (1929).
- (11) HURD: Ind. Eng. Chem. **26**, 50 (1934).
- (12) KASSEL: J. Phys. Chem. **34**, 1166 (1930).
- (13) KASSEL: J. Chem. Physics **1**, 749 (1933).
- (14) LEERMAKERS: J. Am. Chem. Soc. **56**, 1537, 1899 (1934).
- (15) MAREK AND NEUHAUS: Ind. Eng. Chem. **25**, 516 (1933).
- (16) NEUHAUS AND MAREK: Ind. Eng. Chem. **24**, 400 (1932).
- (17) PANETH AND HOFEDITZ: Ber. **62**, 1335 (1929).
- (18) PANETH AND LAUTSCH: Ber. **64**, 2702 (1931).
- (19) PANETH AND LAUTSCH: J. Chem. Soc. **1935**, 380.
- (20) RAMSPERGER: J. Am. Chem. Soc. **50**, 714 (1928).
- (21) RICE, F. O.: J. Am. Chem. Soc. **53**, 1959 (1931).
- (22) RICE, F. O.: Trans. Faraday Soc. **34**, 247 (1934).
- (23) RICE, F. O., AND GLASEBROOK: J. Am. Chem. Soc. **55**, 4329 (1933); **56**, 2381 (1934).

- (24) RICE, F. O., GREENBERG, WATERS, AND VOLLRATH: *J. Am. Chem. Soc.* **56**, 1700 (1934).
- (25) RICE, F. O., AND HERZFELD: *J. Am. Chem. Soc.* **56**, 284 (1934).
- (26) RICE, F. O., AND JOHNSTON: *J. Am. Chem. Soc.* **56**, 214 (1934).
- (27) RICE, F. O., JOHNSTON, AND EVERING: *J. Am. Chem. Soc.* **54**, 3529 (1932).
- (28) RICE, F. O., AND RICE, K. K.: *The Aliphatic Free Radicals*. The Johns Hopkins Press, Baltimore (1935).
- (29) RICE, F. O., AND RODOWSKAS: *J. Am. Chem. Soc.* **57**, 350 (1935).
- (30) RICE, F. O., RODOWSKAS, AND LEWIS: *J. Am. Chem. Soc.* **56**, 2497 (1934).
- (31) RICE, F. O., AND VOLLRATH: *Proc. Nat. Acad. Sci.* **15**, 702 (1929).
- (32) RICE, O. K., AND RAMSPERGER: *J. Am. Chem. Soc.* **49**, 1617 (1927); **50**, 617 (1928).
- (33) RICE, O. K., AND SICKMAN: *J. Am. Chem. Soc.* **56**, 1444 (1934).
- (34) SCHNEIDER AND FROHLICH: *Ind. Eng. Chem.* **23**, 1405 (1931).
- (35) STAUDINGER AND KUPFER: *Ber.* **45**, 508 (1912).
- (36) SICKMAN AND ALLEN: *J. Am. Chem. Soc.* **56**, 1251 (1934).
- (37) STEACIE AND SHAW: *J. Chem. Physics* **2**, 243 (1934).
- (38) STEACIE AND SHAW: *Proc. Roy. Soc. London* **146A**, 388 (1934).
- (39) TAYLOR: *Proc. Am. Phil. Soc.* **65**, 90 (1926).
- (40) TAYLOR AND JONES: *J. Am. Chem. Soc.* **52**, 1111 (1930).
- (41) WINKLER AND HINSHELWOOD: *Proc. Roy. Soc. London* **149A**, 340 (1935)



# THE ACTIVATED COMPLEX AND THE ABSOLUTE RATE OF CHEMICAL REACTIONS

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Since the first measurement of the rate of a chemical reaction by Wilhelmy (32) in 1850 chemists have been struggling with the question of mechanism. Table 1 indicates the progress of this search for guiding principles and gives the names of some of the individuals who contributed, the concepts they proposed, the rate equation if one was suggested, and the year the work was done. The list is of necessity incomplete, and the contributions recorded differ greatly in importance; in certain cases they are only slightly or perhaps even less important than contributions that have been omitted. The field of chain reactions is treated in this symposium by F. O. Rice and so is not considered here.

The thermodynamic-like considerations of van't Hoff (30) were followed by Arrhenius's concept of an activated molecule. Then in 1911 Scheffer and Kohnstamm suggested the idea of an entropy of activation; this was followed in 1918 by the calculations of W. C. McC. Lewis, which equate the rate of a bimolecular reaction to the number of activated collisions. In 1922 Lindemann suggested delayed decomposition in unimolecular reactions as an alternative to the radiation hypothesis. Brønsted in 1923 gave a theory of the effect of the solvent on reaction rates in terms of a rate for the infinitely dilute solution multiplied by the activity coefficients of the reactants over that for an intermediate complex. Beginning in 1926 Lindemann's suggestion bore fruit in the works of Hinshelwood, Rice and Ramsperger, and Kassel, who developed the theory for the decrease of unimolecular rates with pressure. Polanyi and Wigner then treated reaction rates from the point of view of mechanics, with interesting results.

Then came a development in quite a different direction. London's suggestion that many reactions proceed by an adiabatic process was followed by the actual construction of potential surfaces for reactions by Eyring and Polanyi. These surfaces, although approximate, made it possible for the first time to estimate activation energies and so to answer many questions regarding mechanism, such as the relative rates of competing reactions. These surfaces also provided the means for forming a clear picture of the

TABLE 1  
*Development of theory of absolute reaction rates*

NAME AND DATE	REFERENCE	CONCEPT STRESSED AND EQUATION SUGGESTED
Arrhenius (1889)	(1)	Activated molecules $\ln k = B - \frac{A}{T}$
Trautz (1908)	(29)	Activated molecules
Scheffer and Kohnstamm (1911)	(27)	Entropy of activation
W. C. McC. Lewis (1918)	(15)	Molecules reacting = molecules colliding $\times e^{-\frac{E_0}{kT}}$
Polanyi (1920)	(33)	The statistical probability of the collided state substituted for collision number
Rideal (1920)	(24)	} Quantization $E - \frac{E}{kT}$ $k_u = \frac{1}{h} e^{-\frac{E}{kT}}$
Dushman (1921)	(4)	
Brönsted (1922)	(3)	Thermodynamic theory of solvents $k = H \frac{f_1 f_2 \dots}{f^*}$
Rodebush (1923)	(25)	Vibration frequency likened to a collision $k_u = \nu e^{-\frac{E}{kT}}$
Herzfeld (1925)	(9)	Mechanics of decomposition of diatomic molecule $k_u = \nu e^{-\frac{E}{kT}}$

Lindemann Lewis and Smith Hinshelwood Rice and Ramsperger Kassel (1922)	(16) (14) (10) (22) (11)	Delay in decomposition of activated molecules $k_u = e^{-\frac{E}{kT}} \left( \frac{E}{kT} \right)^{s-1} \frac{1}{(s-1)!}$
Tolman (1927)	(28)	Applicability of statistical mechanics to rates $k_u = \frac{\sum k_a p_a e^{-\frac{E_a}{kT}}}{\sum p_i e^{-\frac{E_i}{kT}}}$
Polanyi and Wigner (1928)	(20)	Mechanical considerations of unimolecular reactions $k_u = \nu e^{-\frac{E}{kT}}$
London (1928)	(17)	Reaction frequently an adiabatic process
Eyring and Polanyi (1930)	(8)	Potential surfaces for activated complexes
Pelzer and Wigner (1931)	(19)	The absolute rate of a simple reaction is calculated for the first time $k_u = 2.1 \times 10^6 T^{\frac{2}{3}} \frac{W_0}{kT} e^{-\frac{E}{kT}}$
Wigner (1932)	(31)	Corrections for barrier leakage given $K_u = \frac{4m \left( \frac{n+1}{2} \right)^{\frac{n+1}{2}} \pi^{n-1} e^{-\beta V_0}}{2\beta^{n+1} (A_1 A_2 \dots A_n)^{\frac{1}{2}}} \left\{ 1 - \frac{h^2 \beta^2}{24m} (A_1 + \dots + A_n) \right\}$
La Mer (1933)	(12)	Entropy and free energy of activation. Theory of change of activation energy with temperature $k = (\text{number of collisions}) e^{\frac{S_{\text{act}}}{R}} e^{-\frac{H_{\text{act}}}{kT}}$



TABLE 1—Concluded

NAME AND DATE	REFERENCE	CONCEPT STRESSED AND EQUATION SUGGESTED
Rodebush (1933)	(26)	<p>Thermodynamics and the kinetics of gaseous reactions</p> $\ln K = -\frac{Q_1}{RT} + \ln \left[ \frac{3}{2} \frac{1}{\pi} \left( \frac{m_1 + m_2}{m_1 m_2} \right)^{\frac{1}{2}} \frac{1}{v^2 (kT)^{\frac{1}{2}}} \right]$
Rice and Gershinowitz (1934)	(21)	<p>For molecules to react they must lie in a certain fraction of the total phase space</p>
Eyring (1935)	(6)	<p>For a reaction in any phase of any order (in which the slow process is passage over an energy barrier) there is an activated complex much like an ordinary molecule except for a fourth translation</p> $K = \kappa \frac{F_0 e^{-\frac{E_0}{kT}}}{F_n} \left( \frac{kT}{2\pi m} \right)^{\frac{1}{2}} = \frac{\kappa F_0^{\ddagger}}{F_n} e^{-\frac{E_0}{kT}} \frac{kT}{h}$

detailed mechanical behavior of a reacting system; how the activation energy is distributed between translation and vibration and the precise nature of the activated complex. The surface for three hydrogen atoms was used by Pelzer and Wigner as the basis for the first successful calculation of the absolute rate of a chemical reaction.

Next a calculation of the temperature dependence of the activation energy was made by La Mer, based on the earlier work of Tolman. This was very soon followed by the work of Rodebush, in which he extended an earlier paper and pointed out the usefulness of the conception of an entropy as well as a heat of activation. Neither of the latter authors gave a general theory of the absolute rate of chemical reaction. Rice and Gershinowitz

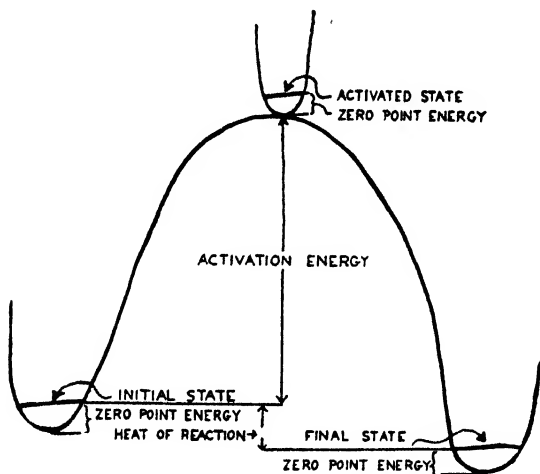


FIG. 1. Energy profile of path of reacting system on many dimensional surface

set out to remedy this situation for bimolecular association reactions. They assumed, correctly, that for a reaction to take place the system must lie in a certain fraction of phase space. This led them to some very interesting results. Because of their method of approach, however, they failed to realize the full significance of the potential surface in defining the precise nature of the activated complex, and so did not give a general equation for the rate of a reaction. All the equations given which are correct, including the very interesting one of Brönsted, arise as specializations of a general theory.

We will now give the general theory for the rate of any reaction in any phase for which the slow process is the passage over a potential energy barrier. The basic conceptions gained from a consideration of the potential surfaces are the following. The activated complex has very nearly

the properties of an ordinary molecule except that instead of having only the three regular translational degrees of freedom it has a fourth, along which it first approaches the barrier, crosses it, and then flies to pieces. Since the activated complex when represented as a point on a potential surface is at a minimum for all the internal degrees of freedom except the one degree of translation for which it is a maximum, we can apply the theory of small vibrations in the same way used for stable compounds. Figure 1 shows in section the path of a point representing our reacting system moving along the many dimensional potential energy surface. The rate of a reaction is given by the equilibrium number of activated complexes per unit of length normal to and near the top of the potential barrier multiplied by the average velocity of crossing the barrier. Thus we have for the rate constant  $k$ , for a reaction of any order in any phase

$$k_i = \kappa K^* \frac{(2\pi mkT)^{\frac{3}{2}}}{h} \sqrt{\frac{kT}{2\pi m}} = \kappa K^* \frac{kT}{h} \quad (1)$$

where  $K^* \frac{(2\pi mkT)^{\frac{3}{2}}}{h}$  is the equilibrium constant between the activated complex (having four translational degrees of freedom) and the reactants; this multiplied by the velocity of crossing the barrier  $\sqrt{\frac{kT}{2\pi m}}$  and by the probability  $\kappa$  of not returning gives the specific reaction rate  $k_i$ . Here  $K^*$  is the equilibrium constant for a hypothetical molecule exactly like the activated complex, except that for convenience we think of the fourth translation as replaced by a stiff vibration. We now define an entropy of activation  $S^*$  and a heat of activation  $H^*$  by the equation

$$K^* = e^{\frac{\Delta S^*}{R}} e^{-\frac{\Delta H^*}{RT}} \quad (3)$$

Introducing equation 3 in equation 1 gives

$$k_i = \kappa e^{\frac{\Delta S^*}{R}} e^{-\frac{\Delta H^*}{RT}} \frac{kT}{h} \quad (4)$$

The theory for a rate process involving a change of phase such as adsorption, vaporization, or sublimation is contained in the first form of equation 1, for which cases  $\kappa$  is to be identified with the accommodation coefficient. The equilibrium constant  $K^*$  can be written also as the ratio of a partition function for the activated complex divided by a partition function for the reacting molecules (6) and the theoretical methods available for any equilibrium apply and are sufficient for calculating  $K^*$  providing we know our potential surface fairly well. In general, because a part of the systems cross the barrier only to collide with the surface and recross in the reverse direction, we must introduce the proper fraction  $\kappa$ . The transmission co-

efficient  $\kappa$  is just the ratio of systems crossing the barrier to systems reacting, and for many simple reactions has approximately the value unity.  $\kappa$  is particularly interesting in that it is the one factor under consideration not deducible from straightforward statistical mechanics. To obtain it theoretically we must solve a problem in mechanics. Fortunately, as stated for many reactions we make a negligible error by taking it as unity.

That the theory does in fact agree precisely with experiment for simple gas reactions is shown by the calculations of Pelzer and Wigner (19) for the ortho-para conversion, and by the calculations with Wheeler and Topley, not yet published, for this reaction and for the reactions  $\text{Br} + \text{H}_2$  and  $\text{H}_2 + \text{I}_2$ . The general theory outlined here differs from that of Pelzer and Wigner and of Wigner (31) in a number of ways, but perhaps the most important is in the explicit account it takes of the rotations of the system. In many problems this is of fundamental importance. How successfully this theory resolves the problem of trimolecular reactions is shown in a paper by the author and Gershinowitz, so that this point need not be discussed further now. Instead the adaptation of the theory to reactions in condensed phases will be considered.

We will, in fact, be largely concerned with a thermodynamic discussion of the equilibrium constant  $K^*$  for the activated complex.

As in ordinary equilibria, in order that the equilibrium constant  $K^*$  be really a constant we must define it as belonging to some standard state. The particular state chosen as standard is not very important, and we shall in fact use different standard states as convenience may dictate, being, however, careful to designate in each case what the standard state is. The dilute gas has one very great advantage as a primary standard if we propose to use statistical mechanics to calculate  $K^*$ . This is because we can then restrict our considerations to the internal coördinates and the distances between the molecules actually reacting, which in the present condition of the theory of condensed phases is important. Choosing this standard we then define the activity  $a_i$  of the molecule  $A_i$  as equal to its concentration at low pressures. For high pressures or condensed phases we introduce an activity coefficient  $\alpha_i$ , such that  $c_i \alpha_i = a_i$ . For the activated complex these quantities are starred thus  $a^*$ ,  $c^*$ ,  $\alpha^*$ . Now

$$\text{the rate of any reaction} = \kappa c^* \frac{kT}{h} \quad (5)$$

But

$$K^* = \frac{a^*}{a_1 a_2 \cdots} \frac{\alpha^* c^*}{\alpha_1 c_1 \alpha_2 c_2 \cdots}$$

whence

$$c^* = K^* \frac{\alpha_1 \alpha_2 \cdots}{\alpha^*} c_1 c_2 \cdots$$

Substituting in equation 5 we get

$$\left( \kappa K^* \frac{\alpha_1 \alpha_2 \cdots}{\alpha^*} \right) c_1 c_2 \cdots$$

Dividing by the concentration of reactants we have for the specific reaction rate

$$k_i = \kappa \left( K^* \frac{\alpha_1 \alpha_2 \cdots}{\alpha^*} \frac{kT}{h} \right) \quad (6)$$

If now we want to introduce as a secondary standard state that of the infinitely dilute solution, we next write

$$\alpha_i = \beta_i f_i,$$

where  $\beta_i c_i$  is the concentration of the vapor of the molecule  $A_i$  over its dilute solution of concentration  $c_i$ , and  $f_i$  is the usual activity coefficient referred to dilute solution. Then

$$k_i = \left( K^* \kappa \frac{\beta_1 \beta_2 \cdots}{\beta^*} \frac{kT}{h} \right) \frac{f_1 f_2 \cdots}{f^*} \quad (7)$$

which is Brönsted's equation, except that now we have a complete theory for the quantity in parenthesis.

We are now in a position to define more closely the intermediate complex to which Brönsted's equation refers. It is a molecular aggregate which is first forming and then exploding at a velocity of about  $10^{-5}$  cm. per second along a particular internal normal coördinate. The potential surface properties only stay approximately constant for a distance of a few tenths of an Ångström unit, giving our activated complex a mean life of  $10^{-14}$  to  $10^{-13}$  second. If there is appreciable interaction between the normal coördinates of the activated complex such a short life will give, instead of sharp energy levels, the fuzzy quantization observed in predissociation. For sharp quantization we should use in our statistics the energy levels of quantum mechanics, while for unsharp levels we can do this or use classical theory. The isotopes provide the best available tool for determining how big the half-quanta of the activated state are, and this will vary from case to case. Degrees of freedom but slightly altered in a reaction will have their normal half-quanta in the activated complex. The results of Bach, Bonhoeffer, and Moelwyn-Hughes (2) for  $\text{Br} + \text{H}_2$  and  $\text{Br} + \text{D}_2$  seem to indicate not very sharp quantization for such simple activated complexes. This is a problem in which Kassel is much interested, as he

informed me privately. It is a problem which was carefully considered during the writing of a previous paper, but still requires consideration. This problem is closely connected with quantum mechanical leakage through a potential energy barrier which has the effect of adding a term to the equation we are using for the rate, as the equation given by Wigner (31) shows. The theoretical potential surfaces and the experiments both indicate this is in general a very small effect. Finally a change in multiplicity may occur as in the famous unimolecular decomposition of nitrous oxide, which introduces another type of chemical inertia. For the great majority of reactions these latter effects are either non-existent or of decidedly secondary importance. They do, however, possess a very great theoretical interest. If we know the  $\alpha$ 's of equation 6 we have a complete theory for the number of collisions in solution in terms of the theory for collisions in the gas phase.

We now consider certain applications of our equations to solutions. From Langmuir's (13) considerations on vapor pressure it can be shown that for any substance forming a perfect solution  $\alpha$ , which is equal to the concentration in the gas divided by the concentration in the pure liquid, is approximately equal to

$$5T^{\frac{1}{2}} e^{-\frac{\Delta H}{RT}}$$

This same value of  $\alpha$  holds for a perfect solution. For a unimolecular reaction our general equation takes the form

$$k_1 = \kappa K^* \frac{kT}{h} \frac{\alpha}{\alpha^*}$$

By our definition of the standard state  $\alpha/\alpha^* = 1$  for the gas. Applying this equation to the decomposition of saturated solutions of nitrogen pentoxide in nitromethane, carbon tetrachloride, and nitrogen tetroxide the results of Eyring and Daniels (7) give  $\alpha/\alpha^* = 1.71, 2.32, \text{ and } 2.01$ , respectively, at  $15^\circ\text{C}$ . The concentration of nitrogen pentoxide in nitromethane is 740 and in carbon tetrachloride 1108 times the concentration in the vapor. These large numbers are therefore the values we must take for  $\alpha$  with  $\alpha^*$  only slightly smaller. These solvents thus shift the equilibrium  $K^*$ , so that it favors the activated complex by a small amount. Nitrogen pentoxide does not decompose inside a crystal, so that  $\alpha/\alpha^* = 0$ . Since  $\alpha$  is not very different than for a saturated liquid it follows that the activity coefficient  $\alpha^*$  of the activated complex is very large. This is just another way of saying that the activated complex is not isomorphous with the normal molecules and so cannot be formed without disrupting the crystal, which would involve a prohibitive activation energy. Thus in general

the neighboring molecules inside a crystal are very effective negative catalysts.

We now consider a different point. Knowing the experimental rate and the heat of activation, our theoretical equation enables us to solve for the entropy of activation. The transmission coefficient is set equal to unity, as it can hardly differ materially from this value in the reactions to be considered. The experimental equation for the decomposition of nitrogen pentoxide is

$$k = 5.08 \times 10^{13} e^{-\frac{24,700}{RT}}$$

Equating this to the theoretical equation we obtain the result that the activated complex is 4.27 units richer in entropy than the normal molecules. This is a typical result for many unimolecular reactions. We now consider some very different cases. The examples to be used are drawn from a paper with Wynne-Jones, which treats the whole theory of rates in condensed phases in more detail. The decomposition of triethylsulfonium bromide into diethyl sulfide and ethyl bromide, as shown by table 2, proceeds at a normal rate at a temperature of 66°C., in spite of the very high activation energy of 35,000 calories. In the column marked  $\Delta S$  is given the total increase of entropy for the reaction.  $\Delta S^*$ , on the other hand, is the entropy of activation calculated from our theory. The agreement is striking. For this unimolecular reaction the activated complex, instead of being like the reactants, has an entropy almost exactly equal to the product molecules. If we measured the reverse bimolecular reaction and interpreted it as a collision process we would be led to ludicrously large collision diameters,—about seven times ordinary diameters. Actually the forces between the molecules do not necessarily extend to larger distances than usual. The large entropy of the activated complex can arise just as well from comparatively free relative vibration and rotation of the constituent diethyl sulfide and ethyl bromide.

We next consider a bimolecular reaction (see table 3) which proceeds many times more slowly than would be expected. This is the combination of dimethylphenylamine with methyl iodide to give the quaternary ammonium salt. Gaseous bimolecular associations under the condition of concentration, etc., which are taken as standard for the specific reaction rate constant, often involve an entropy decrease of about 14 entropy units with a corresponding decrease of about 7 units for forming the intermediate activated complex. For this reaction, however, the one equilibrium measured shows a decrease of 54 entropy units, so that the corresponding decrease of 37 units for the activated complex, although extremely large, might have been anticipated. Predictions for reaction kinetics in the future will probably be largely based on known entropy changes for analo-

gous equilibrium processes rather than on calculations of the number of collisions,—a procedure which ignores all degrees of freedom except those which are initially translations.

As a final example we will use our general theory to calculate the steric factor for one of the elementary processes of chain reactions postulated by F. O. Rice (23). The reaction is the formation of a five-membered ring and a methyl radical from the normal hexyl radical. The activated complex will be an almost closed five-membered ring with a methyl group in the act of leaving the ring. From Parks and Huffman's (18) book on free energy we find that the entropy of cyclopentane is about 21 units less than

TABLE 2

*Decomposition of triethylsulfonium bromide in benzyl alcohol-glycerol mixtures*

*T = 353° Absolute*

PER CENT ALCOHOL	$\Delta S$	$\Delta S^*$	$\Delta S - \Delta S^*$
100	20 85	20 42	0.43
90 23	17 25	15 86	1 39
80 39	13 14	12 91	0 23
69 39	6 80	11 07	-4 27

From data of Corran (Trans. Faraday Soc. 23, 605 (1927)) given by Soper in Discussion of the Chemical Society, 1931.

TABLE 3

*Reaction of dimethylphenylamine with methyl iodide*

*T = 333° Absolute*

SOLVENT	$H^*$	$-S^*$	$-S$
$C_2H_5Cl_4$ .....	11,680	39 48	54 1
$C_6H_5NO_2$ .....	13,020	37 45	
$C_6H_5CH_2OH$ ..	14,400	27 90	
With $C_2H_5I$ in $(CH_3)_2CO$ . . . . .	13,680	38 83	

Data from Essex and Gelormini (5).

that for pentane at 25°C. The formation of the ring changes four rotations into vibrations, so that the difference in entropy should increase with temperature approximately as  $\frac{4}{3}R \ln T$ . This leads us to calculate an entropy decrease from this ring closure of about 25.6 units at 650°C., which corresponds to a steric factor of  $2.5 \times 10^{-6}$  as compared with Rice's estimate of  $10^{-6}$ . Our calculation, although approximate, is right as regards order of magnitude. Thus this point of view leads us to a quantitative theory of the change of the steric factor with temperature, something not possible with the previous ideas for calculating reaction rates.

I shall not take time for more examples, but it should be clear that in all



chemical reactions we must begin thinking of an activated complex which is very much like an ordinary molecule except that it has a fourth translational degree of freedom. This activated complex is not the old one most of us are in the habit of thinking about, which when formed was equally apt to decompose into reactants or products, but rather it is one for which the rate in the forward direction is entirely unaffected by how many activated complexes are proceeding in the reverse direction. This is because the two processes "happen in different coördinates," much like two trains passing on different tracks. Thus the use of equilibrium statistics to count the number of molecules decomposing is unaffected by how far the system is from equilibrium or how fast the reverse reaction is occurring. To be sure, if there is autocatalysis we have a new elementary process with its particular activated complex to be treated exactly as any other elementary process.

In the brief time available I have outlined a general theory of reaction rates, which includes the earlier theories as special cases. I hope that this discussion will have conveyed some idea of the power of this method of attack and the kind of problems which remain to be solved.

#### REFERENCES

- (1) ARRHENIUS: *Z. physik. Chem.* **4**, 226 (1889).
- (2) BACH, BONHOEFFER, AND MOELWYN-HUGHES: *Z. physik. Chem.* **27B**, 71 (1935).
- (3) BRÖNSTED: *Z. physik. Chem.* **102**, 169 (1922); **115**, 337 (1925).
- (4) DUSHMAN: *J. Am. Chem. Soc.* **43**, 397 (1921).
- (5) ESSEX AND GELORMINI: *J. Am. Chem. Soc.* **48**, 882 (1926).
- (6) EYRING: *J. Chem. Physics* **3**, 107 (1935).
- (7) EYRING AND DANIELS: *J. Am. Chem. Soc.* **52**, 1472 (1930).
- (8) EYRING AND POLANYI: *Z. physik. Chem.* **12B**, 279 (1931).
- (9) HERZFELD: *Kinetische Theorie der Wärme*, p. 197. Vieweg und Sohn, Braunschweig (1925).
- (10) HINSHELWOOD: *Proc. Roy. Soc. London* **113A**, 230 (1926).
- (11) KASSEL: *J. Phys. Chem.* **32**, 225 (1928).
- (12) LA MER: *J. Chem. Physics* **1**, 289 (1933).
- (13) LANGMUIR: *J. Am. Chem. Soc.* **54**, 2798 (1932).
- (14) LEWIS, G. N., AND SMITH, D. F.: *J. Am. Chem. Soc.* **47**, 1508 (1925).
- (15) LEWIS, W. C. McC.: *J. Chem. Soc.* **113**, 471 (1918).
- (16) LINDEMANN: *Trans. Faraday Soc.* **17**, 598 (1922).
- (17) LONDON: *Sommerfeld Festschrift*, p. 104. S. Hirzel, Leipzig (1928).
- (18) PARKS AND HUFFMAN: *Free Energies of Some Organic Compounds*. The Chemical Catalog Co., Inc., New York (1932).
- (19) PELZER AND WIGNER: *Z. physik. Chem.* **15B**, 445 (1932).
- (20) POLANYI AND WIGNER: *Z. physik. Chem.*, Haber Band, **139A**, p. 439 (1928).
- (21) RICE AND GERSHINOWITZ: *J. Chem. Physics* **2**, 853 (1934).
- (22) RICE AND RAMSPERGER: *J. Am. Chem. Soc.* **49**, 1617 (1927); **50**, 617 (1928).
- (23) RICE AND RICE: *The Aliphatic Free Radicals*, p. 85. The Johns Hopkins Press, Baltimore (1935).

- (24) RIDEAL: Proc. Camb. Phil. Soc. **26**, 241 (1921).
- (25) RODEBUSH: J. Am. Chem. Soc. **45**, 606 (1923).
- (26) RODEBUSH: J. Chem. Physics **1**, 440 (1933).
- (27) SCHEFFER AND KOHNSTAMM: Verslag Akad. Wetenschap Amsterdam **19**, 878 (1911).
- (28) TOLMAN: Statistical Mechanics, pp. 259-69. The Chemical Catalog Co., Inc., New York (1927).
- (29) TRAUTZ: Z. Elektrochem. **15**, 692 (1909).
- (30) VAN'T HOFF: Études de dynamique chimique.
- (31) WIGNER: Z. physik. Chem. **19B**, 203 (1932).
- (32) WILHELMY: Pogg. Ann. **81**, 413 (1850).
- (33) POLANYI, M.: Z. Physik. **1**, 90 (1920); Z. Elektrochem. **62**, 228 (1920).



# CHEMICAL KINETICS IN GAS PHASE AND IN SOLUTION

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Chemical reactions in solution are much more abundant than reactions in the gas phase, but they have been thought to involve greater difficulties of interpretation. They are more important from a practical standpoint because the syntheses of organic chemistry, the procedures of analytical chemistry, and all the reactions of biology involve reaction in solution.

From the theoretical standpoint, however, our knowledge of gases is much more complete than our knowledge of solutions. The kinetic theory of gases is well established, and exact mathematical formulas are available for calculating the frequency with which molecules collide. The crystalline state is well understood also, through the development of x-ray methods. But very little is known of the liquid state, and because of its pioneer character this field is intriguing.

The molecules of a liquid are held closely together by van der Waals forces, and in many cases there is undoubtedly an association or combination of molecules. Sometimes this association involves the formation of double molecules, and in other cases there may be larger groupings. Recent progress in the theory of the liquid state seems to indicate that there are statistical deviations in the distribution of molecules and that they are involved in the diffraction patterns produced when a beam of x-rays is passed through a liquid. Very little is known regarding the nature of solution and solvation, and one hardly knows whether to emphasize a physical or a chemical combination of the solute with the solvent.

It would be valuable to compare a given reaction in the gas phase with the same reaction in solution. It would be desirable to take over some of the formulas which have been established in the kinetic theory of gases and apply them to solutions. But direct experimental comparison is extremely difficult for several reasons. The temperature range of solvents is limited by the boiling points of the solvents, and only a few gas reactions are known which proceed with measurable velocity in this temperature range. Many gas reactions are complicated by wall effects. Chains are stopped or initiated at the walls, and a catalytic effect of the walls themselves or of materials deposited on the walls may greatly affect the reaction

rate. In solution, on the other hand, the reactions are complicated by combination with the solvent. In the gas phase the products of the reaction are immediately lost in the mass of independent molecules, whereas in solution the products may be kept by molecular collision very near to their starting places.

It is an open question as to which is simpler for theoretical study,—reactions in the gas phase where wall effects can predominate, or reactions in solution where solvation may be an important factor.

#### AQUEOUS AND NON-AQUEOUS SOLUTIONS

Reactions in aqueous solutions are the most common, and an enormous number of rate measurements have been made. Water is unique in many of its properties, and accordingly it is among the reactions in non-aqueous solutions that the closest relation to gas-phase reactions is to be found.

In water and a few related solvents the dissociation of the solutes into ions becomes a very important factor, which is not ordinarily present in the gas phase and in many of the non-aqueous solvents. In spite of the extra variable of an electric charge, reactions between ions may be simpler because the other factors become relatively less important. Marked success has followed the application of two well-known theories of electrolytes to the problem of velocities of reactions involving ions. It is possible to predict the influence of electrolytes on reaction rates by application of the Debye-Hückel theory, and the Brönsted-Bjerrum theory of intermediate complexes.

Reactions involving ions are known also in the gas phase. They may be produced by radium rays, cathode rays, or electrical discharges, but there seems to be no direct correlation between ionization reactions in gases and in solution. Any correlation that could help in bringing these two fields closer together would lead to further progress.

Many ionic reactions proceed so rapidly that they can not be utilized in the study of chemical kinetics. Electrovalent linkages lead to rather complete ionization, and an ion may be considered an activated molecule which needs no extra energy of activation and accordingly no time lag for accumulating it from molecular collisions. Covalent linkages, on the other hand, require so much energy that reactions which involve their rupture do not ordinarily proceed at a measurable rate in the temperature range in which liquid solvents can exist. This leaves reactions involving coördinate linkages as the most common for study in solution.

#### THE DECOMPOSITION OF NITROGEN PENTOXIDE

The simplest reaction which has been studied directly in the gas phase and in solution is the decomposition of nitrogen pentoxide (2, 3). It is not

a chain reaction and it is free from wall effects. The gas-phase reaction seems to be free from complications, and it has been checked in many laboratories. It is an excellent unimolecular reaction and gives practically the same specific decomposition rate from 50 atmospheres osmotic pressure down to 0.05 mm. gas pressure. Inert solvents have very little effect on the decomposition rate. Liquid nitrogen tetroxide causes the decomposition to proceed about twice as fast as in the gas phase, where vacuum may be considered as the "solvent." In nitromethane the decomposition is slightly slower than in the gas phase. Other solvents give intermediate values, as shown in table 1. The energy of activation is the same within the limits of experimental accuracy.

When 100 per cent nitric acid is used as the solvent the decomposition is much slower and the energy of activation is about 3600 calories greater. This greater energy of activation gives such a large temperature coefficient

TABLE 1

*The specific decomposition rate of nitrogen pentoxide in various solvents*

SOLVENT	VALUES OF $k \times 10^4$			ENERGY OF ACTIVATION
	15°C	20°C	25°C.	
Nitrogen tetroxide .....	0 159	0 344		calories 25,000
Ethylidene chloride ..		0 322		24,900
Chloroform .....		0 274	0 554	24,600
Ethylene chloride ..		0 238	0 479	24,400
Carbon tetrachloride ..		0.235	0.469	24,200
Pentachloroethane ..		0 220	0.430	25,000
Bromine ..	0 114	0 215		24,000
Gas phase .....	0 079	0 165		24,700
Nitromethane .....	0.075			24,500

that decomposition at the lower temperatures is barely detectable. The results may be explained on the assumption that an intermediate complex is formed between nitrogen pentoxide and nitric acid which decomposes more slowly,—i.e., it requires more energy for activation.

In the case of the other solvents listed the solvation is probably slight, and in some cases the solvated molecules of nitrogen pentoxide appear to decompose faster than the unsolvated molecules.

The decomposition in saturated solutions is particularly interesting. The oxygen evolved from the solution, which is a measure of the rate of reaction, is contributed by the unsolvated and the solvated nitrogen pentoxide. When the solutions contain an excess of solid crystals the activities of unsolvated nitrogen pentoxide molecules must be the same in all solvents. This gives an opportunity to separate the behavior of the sol-

vated and unsolvated molecules, and to draw conclusions regarding the relative merits of using concentrations or activities in calculating reaction rates. The activities calculated from vapor pressures should all be the same, but the concentrations vary from 0.01 mole per liter in the gas phase to 4.78 moles per liter in carbon tetrachloride at 15°C. If the solvated molecules do not decompose at all, the rate of decomposition would be the same in all solutions. If the solvated and unsolvated molecules decompose at the same rate, the *specific* decomposition rates would be the same in all solutions. Neither situation is found. The specific decomposition rates are of the same order of magnitude in gas phase and in the inert solvents, a fact which indicates that concentrations are more significant than activities in calculating reaction rates. In nitric acid solution the case is different, and further investigation is in progress.

#### BIMOLECULAR REACTIONS

It would be highly desirable to study a bimolecular reaction in both gas phase and solution, as has been done for the unimolecular decomposition of nitrogen pentoxide. Knowing the collision frequency in the gas phase and the specific reaction rates and the energies of activation in the two media, it should be possible to make a direct calculation of the frequency of collision in solution. Unfortunately it is extremely difficult to find an uncomplicated, bimolecular reaction which goes by the same mechanism in the gas phase and in solution. Research in this direction is important.

An idea of the difficulties of such research may be gathered from the interaction of oxalyl chloride and water (4), which occurs both in the gas phase and in inert solvents. In carbon tetrachloride solution it is an excellent second-order reaction, but in the gas phase it is of a definite fractional order, suggesting a chain reaction. The value of the specific velocity constant varies with the initial concentration, and a solid product is produced as an intermediate step and condensed temporarily on the walls of the vessel. In the gas phase the reaction is more exothermic than in solution, and the conditions are more favorable for chain reactions. In spite of all these complications it can be stated that the specific decomposition rate in the gas phase is several powers of ten faster than the reaction in carbon tetrachloride solution. This fact may be significant or it may simply mean that the mechanisms in the two cases are quite different. This unsatisfactory state of affairs is quite common when one tries to compare a gas phase reaction with the same reaction in solution.

#### THE DECOMPOSITION OF TRICHLOROACETATES

It has been known for some time that various solutions of trichloroacetic acid decompose according to a good first-order reaction in the neighborhood

of 100°C. to give carbon dioxide and chloroform. A much higher temperature is required for decomposition in the gas phase, and then a different set of products is obtained. The reaction is interesting because it illustrates how in at least one case the solvent effect and a whole mass of complex data can be nicely interpreted.

It has been found (11) that it is the trichloroacetate ion which undergoes unimolecular decomposition, and that the ionizing power of the solvent and the addition of electrolytes affect the rate by determining the effective concentration of the ion. Trichloroacetic acid decomposes in water, aniline, and basic solvents, but it does not decompose in benzene, carbon tetrachloride, glacial acetic acid, and non-ionizing solvents. In water the various salts of trichloroacetic acid decompose at about the same rate, because the dissociation is practically complete. In alcohol the sodium salt gives a first-order reaction throughout, but the barium salt changes its specific reaction rate during the decomposition. An increase in ionic strength through the addition of electrolytes gives an increase in the decomposition rate.

The solvent effect involves the degree of ionization, but it involves also a solvation effect. The solvents in which one would expect the greatest solvation, such as water, give the slowest reaction and the largest temperature coefficient. These effects can be explained on the assumption that in the process of solvation extra energy is evolved, and to effect decomposition of the trichloroacetate ion the energy equivalent to solvation must be supplied in addition to the energy required for decomposition.

#### THE SOLVENT EFFECT

The effect of the solvent in chemical kinetics may be due to a variety of causes. Combination with solvent (solvation) may give an intermediate complex of high stability or low stability, as already explained. If the complex is stable the reaction will go more slowly; if unstable it will go faster. According to a somewhat more indefinite concept the solvent effect may be due to an electrostatic or electromagnetic influence of the solvent on the solute. The solvent effect can sometimes be explained as due to a varying degree of electrolytic dissociation, as in the case of the decomposition of the trichloroacetates.

There are several ways in which a so-called solvent effect may be without any theoretical significance because it is due to secondary complications. For example, bromine dissolved in carbon tetrachloride may react with a certain organic substance rather slowly as bromine molecules, but bromine dissolved in water may react more rapidly as hypobromous acid. The extent to which the carbon tetrachloride or other inert solvent contains dissolved water will determine, under these conditions, the rate of the



reaction. The same type of complication may result from dissolved air. For example, the rate of bromination of cinnamic acid depends on the amount of oxygen dissolved in the solution (1), and the order in which different solvents affect the rate of bromination may depend chiefly on the relative solubilities of atmospheric oxygen.

In still other reactions dissolved alkali from the glass may be an important factor in changing the rate in different solvents. This is particularly true of keto-enol transformations. In still other cases the appearance of a heterogeneous phase may lead to erratic changes in velocity which are not fundamental. For example, it was found (4) that the chilling of the carbon tetrachloride solution of oxalyl chloride and water led to a great increase in reaction rate. This unexpected behavior was traced to the precipitation of water droplets at the low temperature, and this colloidal water remained for a long time after the solution was again heated. Other solvent effects can sometimes be traced to chain-stopping properties of the solvent or of impurities which it contains.

It is an important question, not yet fully decided, whether or not most of the so-called solvent effects are due to secondary complications such as have been suggested. If the solvent effects can be rendered comparatively slight by removal of these secondary complications, comparison with the gas reaction may be significant. When secondary complications exist there is no point in trying to compare the reactions in solution with those in the gas phase.

#### CALCULATION OF COLLISION FREQUENCY IN SOLUTIONS

Extensive efforts have been made to provide a means for calculating collisions in the liquid phase. There seems to be good support for the formulas which give the frequency of collisions between molecules of solute. It is a familiar fact that the osmotic pressure of a dilute solution and other related properties can be calculated from the simple gas laws on the assumption that the solute behaves as a gas. It is probably safe to use the standard formula

$$Z_{1,2} = \sigma_{1,2}^2 n_1 n_2 \sqrt{8\pi RT \left( \frac{1}{M_1} + \frac{1}{M_2} \right)}$$

where  $Z$  is the number of collisions per second per cubic centimeter between solute molecules 1 and 2,  $n$  is the number of molecules per cubic centimeter,  $M$  is the molecular weight, and  $\sigma_{1,2}$  is the average diameter of the two different molecules. The molecular diameter can not be determined as accurately as in the case of gases but, fortunately, useful calculations of collision frequencies may be made even when the diameters are inaccurately known. Fairly satisfactory results may be obtained with a formula in-

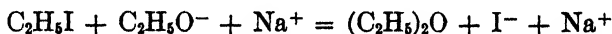
volving the cube root of the molar volume,  $V$ , of the pure liquid or solid solute,

$$\sigma = 1.33 \times 10^{-8} \sqrt[3]{V}$$

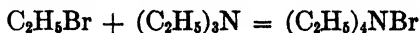
On the basis of collisions calculated in this way Moelwyn-Hughes (7) has examined a large number of bimolecular reactions in solution. He has calculated the specific reaction rate,  $k$ , using the formula

$$k = se^{-E/RT}$$

where  $s$  is the collision frequency of the solute molecules and  $E$  is the energy of activation calculated from the temperature coefficient. He then compares the calculated rate with the observed rate, and if the two agree the reaction has a "normal velocity." In general, reactions between a neutral molecule and a charged ion give normal velocities. An example of this type is the reaction in alcohol solution between an alcoholate and an alkyl iodide such as



Reactions between uncharged molecules are abnormally slow by this criterion. For example, the reaction



in acetone at 60°C. has a calculated specific reaction rate of  $1 \times 10^4$  and an observed value of  $1.7 \times 10^{-4}$ . Other reactions of this general type range from one ten-thousandth to one billionth of the calculated velocity.

This classification is striking. Hinshelwood (5) has suggested that the perturbing influence of an electrically charged ion is necessary to effect successful reaction on collision of activated molecules. It is quite important to extend this examination of normal and slow reactions to radically different types to see if these classifications are completely general. A repetition of some of the earlier experimental work, with special attention paid to the possibility of secondary complications, would also be desirable.

Attempts to calculate the frequency of collision between solute and solvent molecules are much less satisfactory than the calculations of collisions between solute molecules alone. The formulas are given by Moelwyn-Hughes (8). One depends on the viscosity of the solvent, and another on the diffusion coefficient of the solution. Corrections are made for free space between molecules and for other factors. In spite of some experimental checks, these formulas remain of doubtful significance, because the very definition of a collision involving the solvent is uncertain. In the gas phase a collision can be considered as a definite meeting and

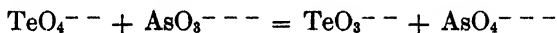
parting of two molecules,—as a collision between billiard balls. In solution a collision is more likely a continuing process, and the solvent probably undergoes persistent or sticky collisions with the solute molecules. The time of collision or the frequency is then rather indefinite.

#### SLOW IONIC REACTIONS

As explained before, reactions between ions are usually immeasurably fast, for example such as the neutralization of acids and bases or the reactions between silver and chloride ions. A few slow ionic reactions are known and their interpretation is interesting.

In some cases a certain orientation of the ions or molecules is necessary in order to effect the reaction. Not every collision of activated molecules is effective, and it is necessary to multiply the collision frequency by a steric factor, less than unity. La Mer (6) has studied reactions of this type, for example, the reaction between  $\beta$ -bromopropionate ion and thio-sulfate ion.

Another slow type involves the transfer of an atom from one ion to the other. Possibly this is a special case of orientation. The oxidation of arsenite by tellurate in aqueous solution at 100°C. is an example (10), as shown by the following equation



A striking relation leading to slow ionic reactions has been pointed out by Shaffer (9). Oxidation-reduction reactions involving two ions are immeasurably fast, but reactions which require triple or quadruple collisions for the stoichiometrical reaction are usually slow. For example the reaction



requires a triple collision for the transfer of the two electrons from a thal-lous ion to two ceric ions. The reaction is very slow. The reduction of ceric ion by ferrous ion is however a fast reaction, for in this case a collision between two atoms is sufficient. The case for the slow oxidation of thal-lous ion is further supported by the fact that manganese ions are excellent catalysts. Manganese ions can exist as  $\text{Mn}^{++}$ ,  $\text{Mn}^{+++}$ , and  $\text{Mn}^{++++}$ , and transfer of the two electrons can be effected by a series of simple collisions, which of course occur much more frequently. Further investigation along this line is important.

The author desires to acknowledge the hospitality of Cornell University where part of this manuscript was written during an appointment as Baker Non-resident Lecturer in Chemistry.

## SYMPOSIUM QUESTIONS

The following questions were suggested for general discussion at the symposium:

1. What is the definition of a collision in solution, and how may collision frequency be calculated?
2. What is the significance of  $a$ ,  $s$ , and  $E$  in  $k = ase^{-E/RT}$ ?
3. Where can more experimental facts be obtained for the direct comparison of reactions in solution and in the gas phase?
4. What is the mechanism by which solvents produce minor differences in the rate of a unimolecular reaction, such as are found with nitrogen pentoxide in inert solvents?
5. Are large solvent effects significant or are they due to secondary complications?
6. Is the formation of "intermediate complexes" of varying degrees of stability frequently responsible for changing reaction rates in different solvents?
7. Should concentrations rather than activities be used in calculating reaction rates, except in the case of ions?
8. Is the requirement for orientation at collision the cause of many slow reactions?
9. Is the requirement for multiple collisions significant in explaining slow ionic reactions?
10. Should bimolecular reactions in solution be classified into (a) reactions between ions and molecules giving normal calculated velocities, and (b) reactions between uncharged molecules giving abnormally slow velocities? What is the theoretical explanation of such a classification?

Insofar as general conclusions may be drawn from the limited discussion it can be stated that questions 6-9 seemed to be answered in the affirmative. Answers to 4 and 10 seemed to be uncertain.

With reference to question 1 there was uncertainty regarding the definition of a collision in solution. It was suggested that the collision frequency may be related to the collision frequency in the gas phase through the partial pressure of the solution.

In question 2 the generally accepted significance of the various terms in the Arrhenius equation for collision frequency, orientation at collision, and energy of activation seemed satisfactory. No suggestion of entirely new meanings for these terms was offered.

No suggestions were forthcoming in question 3 as to favorable reactions for direct comparison of gas phase and solution. The importance of such experimental investigations was emphasized.

Discussion of question 5 was not definite. More experimental facts and new reactions are necessary before the general importance of these secondary complications can be decided.

## REFERENCES

- (1) BAUER, W. H., AND DANIELS, F.: J. Am. Chem. Soc. **56**, 2014 (1934).
- (2) DANIELS, F., AND JOHNSTON, E. H.: J. Am. Chem. Soc. **43**, 53 (1921).
- (3) EYRING, H., AND DANIELS, F.: J. Am. Chem. Soc. **52**, 1472 (1929).
- (4) FUGASSI, J. P.: Ph.D. thesis, University of Wisconsin, 1934
- (5) HINSHELWOOD, C. N.: J. Chem. Soc. **1933**, 1357.
- (6) LA MER, V. K., AND KAMNER, M. E.: J. Am. Chem. Soc. **53**, 2832 (1931).

- (7) MOELWYN-HUGHES, E. A.: Chem. Rev. **10**, 258 (1932).
- (8) MOELWYN-HUGHES, E. A.: The Kinetics of Reaction in Solution Oxford University Press, Oxford (1933).
- (9) SHAFFER, P. A.: J. Am. Chem. Soc. **55**, 2169 (1933).
- (10) STROUP, P. T., AND MELOCHE, V. W.: J. Am. Chem. Soc. **53**, 3331 (1931).
- (11) VERHOEK, F. H.: J. Am. Chem. Soc. **56**, 571 (1934).

# ANOMALOUS TEMPERATURE COEFFICIENTS ASSOCIATED WITH AQUEOUS HALOGEN SOLUTIONS. AN EXPLANATION ASSUMING VARIABLE HYDRATION OF THE HALOGENS

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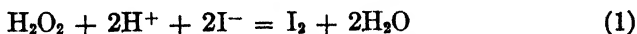
## I. INTRODUCTION

Experimental evidence, new and old, will be presented to show that aqueous halogen solutions generally exhibit temperature coefficients of an unusual kind, for the heat terms associated with many of these temperature coefficients decrease more or less rapidly near 0°C. to approach nearly constant values as the temperature is increased. It will be shown that these anomalies find a quantitative explanation, satisfactory though beset by minor inconsistencies, in the assumption that the region of anomalous temperature coefficients is the region in which the degree of hydration of the halogens is changing. An inductive method of presentation that ignores historical sequence will be adopted, because it is simple, and because it emphasizes the rôle of a kinetic investigation in the rediscovery of the anomalies just mentioned.

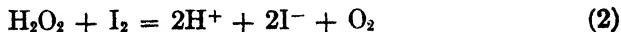
## II. HYDROLYSES OF THE HALOGENS

### *A. Iodine*

Hydrogen peroxide added to an acid solution (23, 24, 27) is at first reduced according to the stoichiometric equation



Conversely, hydrogen peroxide added to an aqueous iodine solution may be oxidized



Once these facts have been established by experiment, it follows that neither reaction can be absolutely isolated so long as its products are not

<sup>1</sup> This paper is a contribution jointly from the Chemical Laboratory of the University of California, where the calculations were completed in 1933, and from the Research Laboratory of the General Electric Company, where the material was recently cast into its present form.

completely removed. If the products of reaction 1 (reaction 2) are permitted to accumulate, then the *relative* rate of reaction 2 (reaction 1) will increase; and, if enough peroxide is present, this increase will continue until a *steady state* has been reached where the two rates are equal, and where the only measurable reaction is the sum of reactions 1 and 2, namely



the decomposition of hydrogen peroxide. By combining data from rate and concentration measurements made at the steady state, it is possible to deduce the specific rates of the compensating reactions 1 and 2. At 25°C., the specific rates thus deduced are in excellent agreement with those obtained for reactions 1 and 2 when each reaction was alone of experimental importance; for reaction 1 it has been shown that this agreement extends over the temperature range from 0 to 50°C. These facts place the deduction from steady state data of the specific rate  $k'_2$  (reaction 2) for temperatures other than 25°C. upon an exceptionally secure foundation.

Within a wide range of experimental conditions the rate of reaction 2 obeys the differential equation<sup>2</sup>

$$-\frac{d(\text{H}_2\text{O}_2)}{dt} = k'_2(\text{H}_2\text{O}_2) \frac{(\text{I}_2)}{(\text{H}^+)^2(\text{I}^-)} \quad (4)$$

which serves to define  $k'_2$ . As the investigation of the effect of temperature variation on  $k'_2$  proceeded, it soon became evident that this rate constant fails completely of obeying the Arrhenius equation at temperatures below 50°C., for in this temperature interval the heat of activation decreases rapidly from 57,000 cal. (this heat term, computed from the 0°C. and 3.5°C. values of  $k'_2$ , corresponds to a 10°C. temperature coefficient of about 40) near 0°C. to 25,000 cal. at the higher temperature. From 50 to 70°C., this heat remains sensibly constant; i.e., the Arrhenius equation is the limiting law which  $k'_2$  approaches as the temperature is increased. This anomalous character of the temperature coefficient of  $k'_2$  was discovered in 1931; it led to an investigation of the literature, and to additional experimental work, in order to reveal whether this behavior is unique or whether

<sup>2</sup> The usual conventions will be employed. Specific rates will be represented by small letters ( $k$ ,  $\kappa$ ); equilibrium constants by capitals ( $K$ ,  $R$ ,  $D$ ). X may mean either Cl, Br, or I—thus, HXO is the formula of a hypohalous acid. ( ) usually denotes "concentration of" in moles per liter.  $\rightarrow$  is restricted to steps that may be rate-determining;  $=$  to stoichiometric equations and to rapid reactions following a rate-determining step. Unit time is the minute. Heats of activation (as contrasted with energies of activation) are the energy terms corresponding to the empirically determined temperature coefficients of the specific rates, and are represented by  $Q$ 's; heats of reaction (thermodynamic quantities) are represented by  $\Delta H$ 's, as is usual.

it is a general phenomenon to be expected for each of the three common halogens.

An examination of this anomalous temperature coefficient (see figure 1) permits certain conclusions to be drawn. While the heat of activation ( $Q$ ) of a chemical reaction is to be regarded in general as a variable quantity, whose change with temperature may give some insight into the mechanism by which activation occurs, the change in figure 1 is obviously not of this type;  $\partial Q/\partial t$  is far too large (it averages over 500 cal. per degree)

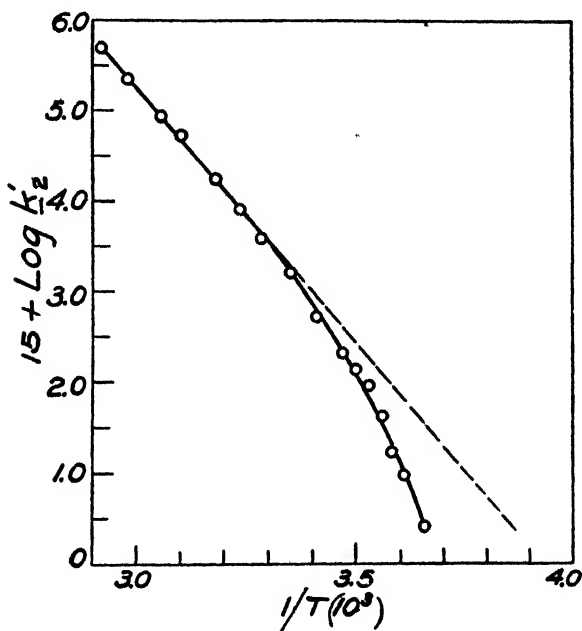


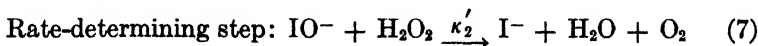
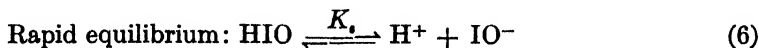
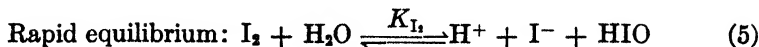
FIG. 1. Anomalous temperature coefficient shown by kinetic data. Effect of temperature change on the specific rate of reaction 2.

and it departs too far from constancy (for it decreases virtually to zero near  $50^\circ\text{C}.$ ). The same reasoning renders it highly improbable that an explanation for this behavior is to be found in the thermodynamic equation  $\partial\Delta H/\partial T = \Delta c_p$ . And finally, the anomaly does not result because reaction 2 is complex in the sense that it involves two or more (parallel and independent) rate-determining steps with different heats of activation; were this the case, the curvature would necessarily have to be convex (not concave) toward the  $1/T$  axis.

In order to proceed further, it is advisable now to assign reaction 2 a definite mechanism in accord with its rate law (equation 4). The most



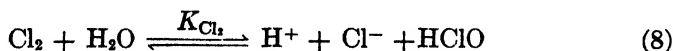
reasonable (though not the only) mechanism that can be thus assigned is (24, 27)



If this mechanism is to give a satisfactory kinetic interpretation to equation 4, the complex specific rate  $k'_2$  must equal the product  $K_{\text{I}_2}K_{\text{I}_2}\kappa'_2$ . At 25°C.,  $k'_2 = 2(10^{-12})$ ,  $K_{\text{I}_2} = 3(10^{-13})$  (6), and  $K_{\text{I}_2} = 2(10^{-11})$  (10); whence  $\kappa'_2 = 3(10^{11})$ . Let us now consider with which of the three reactions composing the above mechanism the decrease of 32,000 cal. in the heat term associated with  $k'_2$  can most plausibly be identified. Rate-determining steps with specific rates so large as  $\kappa'_2$  will scarcely have a large heat of activation; reaction 7 cannot therefore be responsible for this large decrease. The heat of dissociation of hypoiodous acid probably will not exceed, say, 10,000 cal., so that this equilibrium may likewise be eliminated from consideration. Only the hydrolysis equilibrium of iodine (reaction 5) remains. If this analysis of the anomalous temperature variation is correct, the explanation of the anomaly is therefore to be sought in the hydrolysis equilibrium of iodine, the equilibrium constant for which should reveal the curvature recorded in figure 1. Unfortunately, values of this equilibrium constant are not available for a number of temperatures sufficient to make possible a convincing comparison between the results of kinetic measurements (as given in figure 1) and those from equilibrium (in this case, conductivity) measurements made directly on the iodine hydrolysis. Indeed, it is not certain that direct equilibrium measurements accurate enough for this problem can be made near 0°C. because of the small extent to which iodine is hydrolyzed at these temperatures; if  $K_{\text{I}_2}$  does show the curvature given in figure 1, such measurements are probably impossible. In the absence of appropriate equilibrium data for the iodine hydrolysis, similar data for the other halogen hydrolyses are acceptable substitutes.

### B. Chlorine

At the close of the last century Jakowkin (18) concluded his classic investigation of the chlorine hydrolysis,



in which he discovered (by measuring the distribution of chlorine between air and carbon tetrachloride, respectively, and aqueous solutions) that the

heat term associated with  $K_{Cl_2}$  (cf. figure 2, where his data are plotted) does exhibit an anomalous temperature variation of the kind under discussion. In the case of reaction 8 the decrease (from 8000 cal. near 0°C. to 2900 cal. near 50°C.) is relatively even more marked than the corresponding change for reaction 2. There is, however, a marked difference between the two cases; for, as an examination of figure 2 will show, values of  $K_{Cl_2}$  do not fall (as did those of  $k'_2$ ) on a straight line for all temperatures above 50°C.; in fact, there is some doubt as to whether the line in figure 2 represents a limiting law,—as to whether the heat term associated with  $K_{Cl_2}$  is ever constant. Although further consideration of this case is conveniently postponed, it seems well to mention here that Jakowkin himself clearly appreciated this anomalous behavior, for he concluded that the heat of hydrolysis of chlorine decreases markedly with increasing

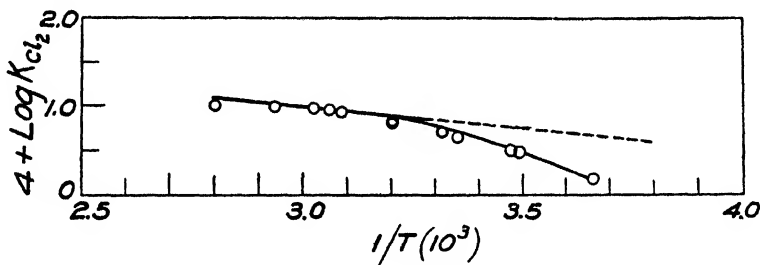


FIG. 2. Anomalous temperature coefficient shown by equilibrium data. Effect of temperature change on the equilibrium constant for the chlorine hydrolysis.

temperature so that it becomes equal to zero between 85 and 95°C. For the present we shall point out only that the temperature variations of the specific rate  $k'_2$  (figure 1) and of the equilibrium constant  $K_{Cl_2}$  (figure 2) are so similar below 50°C. that they must almost certainly be due to the same cause. This fact leaves little doubt that the mechanism given above for reaction 2 is essentially correct, and supports the reasoning which establishes the iodine hydrolysis equilibrium as the most probable source of the failure of reaction 2 in conforming to the Arrhenius equation. We should expect, therefore, that rate-determining steps involving hydrolysis products like  $HXO$  or  $XO^-$  in equilibrium with the halogen  $X_2$  will in general not be governed by this equation, and that the bromine hydrolysis equilibrium also will show departures from the thermodynamic relation

$$\frac{d(\ln K)}{d(1/T)} = \frac{-\Delta H}{R}$$

### C. Bromine

In the case of bromine, kinetic data (for the reaction between bromine and hydrogen peroxide) and equilibrium data (for the bromine hydrolysis)

both show anomalous temperature variations of the kind being discussed. Unfortunately, the deviations from linearity in the plots corresponding to figures 1 and 2 are much smaller for this halogen, with the result that the comparison between these two types of experimental data becomes thereby somewhat less convincing.

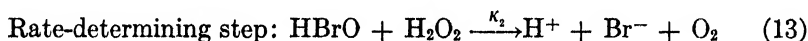
Bray and Livingston (7, 8, 29, 30) in a series of kinetic investigations have demonstrated conclusively that the catalytic decomposition of hydrogen peroxide by the bromine-bromide couple involves only the two compensating reactions



(whose sum is reaction 3) over a wide range of experimental conditions. Both at the steady state and at a distance from it reaction 10 obeys the rate law

$$-d(\text{H}_2\text{O}_2)/dt = k_2(\text{H}_2\text{O}_2) \frac{(\text{Br}_2)}{(\text{H}^+)(\text{Br}^-)} \quad (11)$$

which, except for the inverse hydrogen ion term, is formally identical with equation 4. The authors give



as the most probable mechanism for reaction 10; Makower and Liebhafsky (31) adduced additional (semiquantitative) evidence for this choice when they proved that hypobromous acid in the virtual absence of bromine reacted with hydrogen peroxide at a rate not less than one-tenth that to be expected if  $\kappa_2$  is, as Bray and Livingston have found, somewhat greater than  $10^6$ . The above mechanism for reaction 10 is thus established beyond a reasonable doubt; if the bromine hydrolysis equilibrium, reaction 12, exhibits an anomalous temperature variation, we shall therefore expect to find it reflected in  $k_2$ .

In order to discover whether or not this expectation is realized, rate and concentration measurements for the steady state were made (25) over the largest temperature range (0 to 70°C.) within which accurate results could be obtained. As in the case of iodine, values of the specific rate at different temperatures were deduced from these two sets of data; these values of  $k_2$  are plotted in figure 3. Although the departure from linearity is not large even at 0°C., it is unmistakable; and, in conjunction with the experimental evidence already given for iodine and chlorine, it makes apparent that

$K_{\text{Br}_2}$ , the equilibrium constant for the bromine hydrolysis, ought to show a similar divergence.

The electrical conductivities of aqueous bromine solutions at five temperatures have recently been measured (28) in order to establish whether the corresponding  $K_{\text{Br}_2}$  values do show a departure of this kind. These values, together with those similarly obtained by other investigators, are summarized in table 1.

The experimental results of table 1 are remarkably concordant and warrant the conclusion (28) that "the temperature variation of  $K_{\text{Br}_2}$  becomes anomalous in the neighborhood of 0°; but the departure of  $d(\log K_{\text{Br}_2})/d(1/T)$  from constancy is much less than that observed by Jakowkin in the case of chlorine." This conclusion derives further support from the fact that the temperature coefficients are probably more accurately established than are the absolute values of  $K_{\text{Br}_2}$ ; for these temperature

TABLE 1  
*Summary of  $K_{\text{Br}_2}(10^9)$  values for different temperatures*

INVESTIGATORS	0°C	10°C	25°C	30°C.	35°C.
Bray and Connolly (6). . . . .			5.6*		
Jones and Hartmann (20) . . . . .	0.68*				
Jones and Baekström (19) . . . . .			5.8		
Liebhaufsky (28) (measured). . . . .	0.69	1.76	5.8	8.4	11.3
Liebhaufsky (computed) . . . . .	0.76	1.80	(5.8)†	8.3	(11.3)†

\* Experimental results recalculated by Liebhaufsky to yield this value.

† Value assumed in deriving the equation  $\log K_{\text{Br}_2} = 1.37804 - 2866.1/T$ .

coefficients were obtained for each bromine solution within a short time and without refilling the conductivity cell, so that they are virtually independent (as the absolute values are not) of the presence of conducting substances not produced in reaction 12; the detailed experimental results (reference 12, table 2) clearly show this to be true.

If reaction 10 has been assigned its correct mechanism (equations 12 and 13), if  $d(\log \kappa_2)/d(1/T)$  is sensibly constant, and if the conductivity measurements have been correctly interpreted, then the results in table 1 should show a departure from linearity identical with (not only similar to) that of the rate constants plotted in figure 3. Now, this departure is measured at 0°C. for the  $K_{\text{Br}_2}$  results by  $\log 0.76/0.69 = 0.04$ ; the corresponding quantity for figure 3 is 0.21, the logarithm of the quotient for that temperature of  $k_2(\text{calcd.})/k_2(\text{measd.})$ ,  $k_2(\text{calcd.})$  being the extrapolated value given by the limiting straight line. The difference between 0.04 and 0.21 is too large to be attributed to experimental error, but it can in all likelihood be materially reduced without violating the kinetic

data, by choosing a limiting line of slightly different slope. (As matters stand, no attempt has been made to bring the equilibrium and kinetic measurements into agreement; this could easily be done on the assumption that in figure 3, as in figure 2, the experimental points never quite conform to a limiting line). We conclude provisionally, therefore, that a slight inconsistency exists between the results of figure 3 and those of table 1, which might, if real, compel a reëxamination of the conductivity data to determine whether these have been correctly interpreted or whether some additional equilibrium (like  $\text{Br}_2 \rightleftharpoons \text{Br}^+ + \text{Br}^-$ ) also needs to be taken into

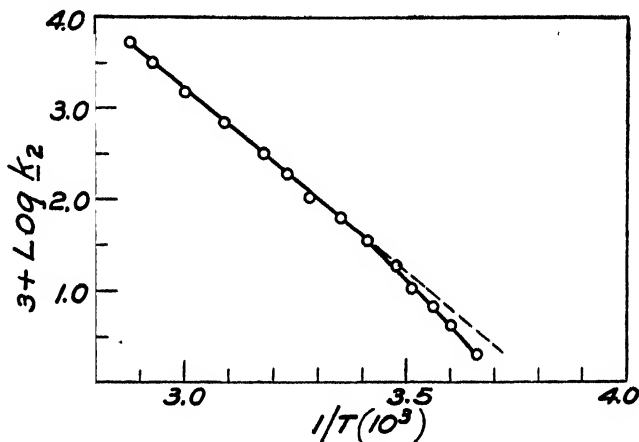


FIG. 3. Anomalous temperature coefficient shown by kinetic data. Effect of temperature change on the specific rate of reaction 10.

account (36). In spite of this inconsistency, however, our main thesis—namely, that aqueous halogen solutions exhibit anomalous temperature coefficients—seems proved by both equilibrium and kinetic measurements for the case of the bromine hydrolysis.<sup>3</sup>

<sup>3</sup> In addition to the two sets of experimental data discussed above, there are available in the case of bromine the following results of kinetic measurements directly on reaction 10:  $\chi_2 = 0.043$  (35°C.), 0.018 (25°C.), and 0.00062 (0°C.). The first two values are based on measurements by Bray and Livingston (8), who recalculated Balint's results to obtain the third.  $\chi_2 = k_2\gamma^2$  (HBr); the activity coefficient term is introduced to compensate the effect of changing ionic strength on the bromine hydrolysis (reaction 12). Since the  $\gamma$  values were assumed to be independent of temperature, the  $\chi_2$  values will yield the same heat of activation as the  $k_2$ 's from which they were derived. From the results for 35°C. and 25°C., we find  $d(\log \chi_2)/d(1/T) = 3473$ , whence  $Q = 15,900$  cal. If  $Q$  remains constant to 0°C., then  $\chi_2$  (calcd.) = 0.00065 at that temperature, a value greater by 5 per cent than 0.00062 =  $\chi_2$  (measd.). This difference of 5 per cent corresponds closely to the departure (which has been discussed above) of  $d(\log K_{\text{Br}_2})/d(1/T)$  from constancy near 0°C.

Unfortunately this excellent agreement cannot be accepted without reservation.

The experimental evidence relating to the hydrolysis equilibria of the halogens is now complete and leads to the conclusion that the heat terms associated with these equilibria all show the same type of anomalous temperature variations. The next logical step is to determine, if possible, whether this anomaly can be "localized,"—i.e., whether it arises from the behavior of the substances (the halogens,  $X_2$ , and water) on the left side of these equilibria as they are written, or from the behavior of those ( $HXO$ ,  $H^+$  and  $X^-$ ) on the right.

### III. DISTRIBUTION OF THE HALOGENS BETWEEN AIR AND WATER

If it can be shown that a set of aqueous halogen equilibria involving a set of products differing from  $HXO$ ,  $H^+$ , and  $X^-$  exhibits anomalous temperature coefficients similar to those for the halogen hydrolyses, then the "localization" will probably have been accomplished; for that would be strong indication that the anomaly arises from the interaction of  $X_2$  and  $H_2O$ , the only two substances common to both sets of equilibria. We shall now summarize the experimental evidence relating to reactions of the type



where

$$D_{X_2} = P_{X_2} \text{ (in atm.)} / (X_2) \text{ (in moles per liter)} \quad (15)$$

Data permitting the calculation of  $D_{X_2}$  for each of the three common halogens as a function of temperature is already in the literature. For iodine, the solubility data given in the International Critical Tables (17) were combined with the results of Baxter and Grose (2) for the vapor pressure of solid iodine (calculating these vapor pressures from more recent equations would have produced no change significant for our purposes). For

---

Bray and Livingston give  $\pm 10$  per cent as the average spread of the  $x_2$  values they have calculated from Balint's data; it is thus not necessary to consider the divergence of their own results to show that the above 5 per cent difference cannot be very securely established, and we must conclude that the  $x_2$  data do not prove reaction 10 to have a variable heat of activation. This conclusion is not incompatible with the statement by Bray and Livingston that the temperature coefficient of reaction 10 (presumably for a  $10^\circ\text{C.}$ -temperature interval) decreases with increasing temperature, since  $\Delta(1/T)$  for any fixed temperature interval decreases with increasing  $T$ , and this causes a reaction with constant heat of activation to have a variable (but not an *anomalous*) temperature coefficient.

Rate measurements at a number of temperatures and for reaction mixtures initially identical in composition should, of course, show reaction 10 to have a variable heat of activation, in agreement with the two sets of data discussed in the text.

chlorine the data of Jakowkin (reference 18, p. 655) were employed. The data for bromine are given in different units by Hantzsch and Vagt (reference 12, p. 726, table 13) in their paper dealing with the solvation of the

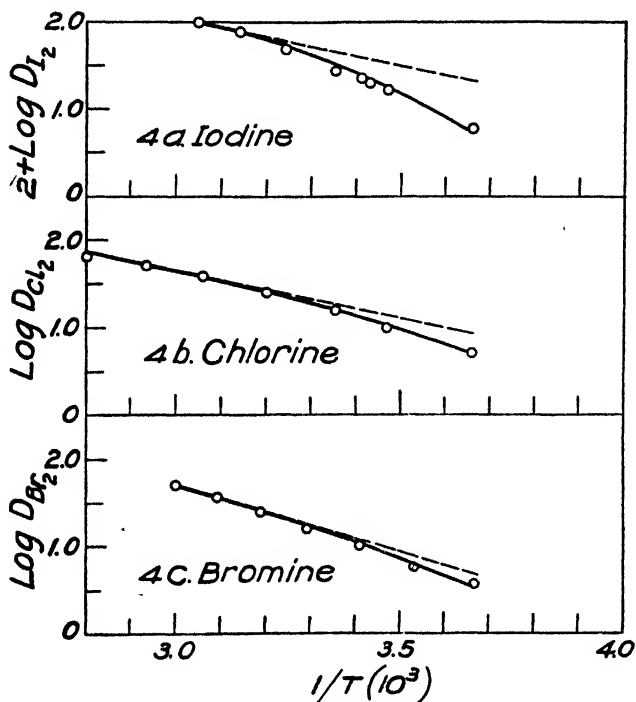


Fig. 4. Anomalous temperature coefficients shown by equilibrium data. Effects of temperature change on the distribution ratios of the halogens between air and water.

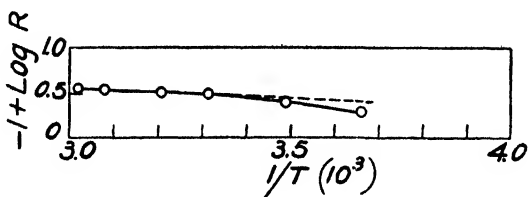


Fig. 5. Anomalous temperature coefficient shown by equilibrium data. Effect of temperature change on the distribution ratio of chlorine between carbon tetrachloride and water.

halogens. In every case the experimentally measured aqueous halogen concentration has been diminished by the equilibrium concentration of the hypohalous acid (a hydrolysis product) to give the true concentration of dissolved halogen. Jakowkin applied this correction himself; for bromine

and iodine it has been made by estimating values of  $K_X$ , (equations 5 and 12), and, since this correction is much less important for these two halogens, the details will not be given.  $D_X$ , as a function of temperature is given for each halogen in figure 4.

An examination of figure 4 immediately reveals its close similarity to the preceding three figures dealing with the halogen hydrolyses; we conclude, therefore, that the anomalies we have been discussing do in fact originate principally in the interaction of the halogens and water. This conclusion is borne out, furthermore, by Jakowkin's values for  $R_{Cl_2} = (Cl_2)_{CCl_4}/(Cl_2)_{H_2O}$ , which are plotted in figure 5 ( $R_{Cl_2}$  is Jakowkin's  $h_1$ ; cf. reference 18, p. 652, table 46, line 6). Many of the data that have been presented graphically will be given later (tables 2 and 3), when an attempt will be made to interpret them quantitatively, in the light of the explanation now to be proposed.

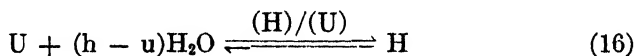
#### IV. AN EXPLANATION OF THE OBSERVED ANOMALIES

It has long been known that the halogens are hydrated, and that these hydrates decompose as the temperature is increased. In 1885 Roozeboom (32) had already completed a quantitative investigation of the dissociation pressures of the solid bromine and chlorine hydrates, to which he assigned the formulas  $Cl_2 \cdot 8H_2O$  (1) and  $Br_2 \cdot 10H_2O$  (9); for both hydrates these pressures increase with the temperature, reaching one atmosphere near  $10^\circ C$ . Although these solid hydrates were discovered over a century ago, their composition is still somewhat uncertain; and the formulas  $Cl_2 \cdot 6H_2O$  and  $Br_2 \cdot 8H_2O$ , "established" after Roozeboom's work, have recently been confirmed, as has the existence of the bromine decahydrate (14). An examination of the literature suggested that two or more solid hydrates differing in stability and in composition may exist for each of these two halogens. A solid hydrate of iodine (34) appears to have been obtained only in the presence of a foreign gas (oxygen, nitrogen) at high pressures (150 to 350 atm.) and at moderate temperatures ( $3$  to  $8^\circ C$ .); this hydrate is remarkable for its surprising color, which unexpectedly differs from that of the brown aqueous iodine solutions by being violet. The same factors, traceable ultimately to its atomic structure, that cause iodine to differ from the other halogens by being a dense solid sparingly soluble in water are probably also responsible for its failure to form a solid hydrate under ordinary conditions. The experimental evidence concerning the solid bromine and chlorine hydrates would lead us to expect that these halogens (if not iodine also) in aqueous solutions at low temperatures will form hydrates to which it may be impossible to assign a single definite formula, and that these hydrates will become increasingly unstable as the temperature is raised.



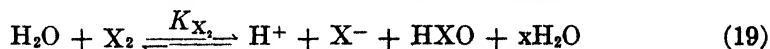
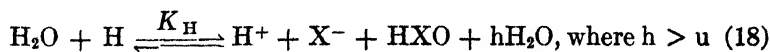
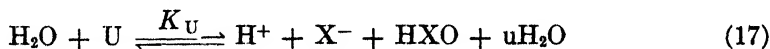
The state of the dissolved halogens is intimately related to the colors of their solutions; not unnaturally, solutions of iodine, whose brilliantly colored vapor undergoes the most marked color change (from violet to brown) when dissolved in certain solvents like water, have been most extensively investigated. These investigations almost without exception support the conclusion that the brown solutions contain solvated iodine (3, 4, 5), and the fact, already recorded in 1890, that this brown color tends to change to violet on heating (37) shows the solvates to be unstable at higher temperatures. We shall discuss the colors of iodine solutions in some detail later; for the present we observe only that the experimental evidence concerning them complements what is known concerning the solid hydrates of bromine and chlorine. Consequently, we may regard all three halogens in aqueous solutions as being hydrated, and the corresponding hydration equilibria as shifting toward the less hydrated forms as the temperature is raised.

The body of past experience is thus entirely in accord with an attempt to explain the anomalous temperature coefficients encountered in aqueous halogen solutions on the assumption that the halogens in these solutions exist in two forms, U and H, differing from each other only in the degree of hydration. The simplest conditions would obtain if U were unhydrated and H had the formula  $X_2 \cdot H_2O$ ; but the argument to be presented does not depend upon the realization of these simplest conditions, so that H may contain any reasonable number of water molecules, so long as it is hydrated to a greater extent than U. The equilibrium between these two forms of  $X_2$ ,



must shift toward U as the temperature is raised in order to conform with the color change (from brown to violet) of many iodine solutions and the dissociation of the solid bromine and chlorine hydrates, both of which are favored by a temperature increase. To test the assumption that the hydration of the halogens leads to anomalous temperature coefficients for their aqueous solutions, we shall at first confine ourselves to the hydrolysis equilibria as examples. The extension of our reasoning to other types of equilibria will involve no difficulty.

If the hydration equilibrium (equation 16) really exists, these hydrolysis equilibria may be written in three ways:



the third of which is the conventional (cf. equations 5, 8, and 12). So long as the hydration equilibrium is established either equation 17 or equation 18 may be used to represent the hydrolysis equilibrium; for  $K_U$  and  $K_H$  are obviously related because

$$(H)/(U) = \text{const. (at constant temperature)} \quad (16a)$$

Since

$$(X_2) = (H) + (U) \quad (20)$$

it follows that  $K_{X_2}$  cannot be a true equilibrium constant if  $(H)$  and  $(U)$  are comparable in magnitude. These considerations are borne out by a comparison of the expressions for the equilibrium constants of reactions 17, 18, and 19:

$$K_U = \frac{(H^+)(X^-)(HXO)}{(U)} \text{ and } K_H = \frac{(H^+)(X^-)(HXO)}{(H)} \quad (17a \text{ and } 18a)$$

$$K_{X_2} = \frac{(H^+)(X^-)(HXO)}{(U) + (H)} \quad (19a)$$

We shall now examine the temperature variation to be expected for  $K_{X_2}$  if  $H$  and  $U$  are always in rapid equilibrium and sometimes of comparable concentration. We shall assume all heats of reaction to be constant and distinguish three regions within the temperature range to be considered.

#### *Region I. The higher temperatures*

The hydration equilibrium (equation 16) is displaced far to the left, so that  $(U) \gg (H)$  while  $(X_2) = (U)$ , very nearly. Then, by equations 17a, 18a, and 19a

$$K_{X_2} = \frac{(H^+)(X^-)(HXO)}{(U)} = K_U \ll K_H \quad (21)$$

and

$$d(\log K_{X_2})/d(1/T) = d(\log K_U)/d(1/T) = -\Delta H_U/4.58 \quad (22)$$

At these temperatures,  $\log K_{X_2}$  plotted against  $1/T$  will therefore yield a straight line, the slope of which measures  $\Delta H_U$ , the heat of reaction 17.

#### *Region III. The lower temperatures*

The hydration equilibrium (equation 16) is displaced far to the right, so that  $(H) \gg (U)$  while  $(X_2) = (H)$ , very nearly. Then, again by equations 17a, 18a, and 19a

$$K_{X_2} = \frac{(H^+)(X^-)(HXO)}{(H)} = K_H \ll K_U \quad (23)$$

and

$$d(\log K_{X_2})/d(1/T) = d(\log K_H)/d(1/T) = -\Delta H_H/4.58 \quad (24)$$

At these temperatures,  $\log K_{X_2}$  plotted against  $1/T$  will therefore yield a straight line, the slope of which measures  $\Delta H_H$ , the heat of reaction 18.

*Region II. The intermediate temperatures*

The two halogen species U and H are present at comparable concentrations. Equations 17a, 18a, and 19a now yield

$$K_U > K_{X_2} = \frac{(H^+)(X^-)(HXO)}{(U) + (H)} < K_H \quad (25)$$

Also,

$$\frac{(H^+)(X^-)(HXO)}{(U) + (H)} \frac{(U) + (H)}{(U)} = K_{X_2}[1 + (H)/(U)] = K_U \quad (26)$$

(A corresponding equation may obviously be written for  $K_H$ ). In this region of intermediate temperatures, (H) is increasing with  $1/T$  at the expense of (U). As this region is traversed toward the direction of lower temperatures (higher values of  $1/T$ ),  $[(H) + (U)]/(U)$  increases rapidly from a value near unity, while  $[(H) + (U)]/(H)$  decreases rapidly to approach that value. Therefore, by equations 17a, 18a, and 19a,

$$\begin{aligned} d(\log K_U)/d(1/T) &= -\Delta H_U/4.58 < d(\log K_{X_2})/d(1/T) \\ &< -\Delta H_H/4.58 = d(\log K_H)/d(1/T) \end{aligned} \quad (27)$$

If all three regions are realized in the case of a hydrolysis equilibrium, the following temperature variation for  $K_{X_2}$  is therefore to be expected: At higher temperatures,  $\log K_{X_2}$  will give a straight line when plotted against  $1/T$ . As  $1/T$  increases, a downward divergence will gradually occur, so that the straight line becomes a curve concave toward the  $1/T$  axis. As  $1/T$  is increased still further, this curve merges into a straight line steeper than the limiting line for higher temperatures. This type of temperature dependence is illustrated in figure 6; comparison of this with the five previous figures shows that the hypothetical curve for regions I and II is qualitatively identical with those describing the actual measurements, but that the realization of region III is doubtful because it does not occur at temperatures sufficiently above  $0^\circ\text{C}$ ., the freezing point of water. Before proceeding to a quantitative test of hydration hypothesis, we observe that the above equations can easily be made applicable to any set of aqueous halogen equilibria; the formulas of the products in the new equilibria must of course replace  $H^+$ ,  $X^-$ , and  $HXO$  in the equations, and the changes in nomenclature which this substitution requires must be made. Since

the concentration of water does not appear in the above equations, they can be readily modified also for the cases of other solvents.

A quantitative test of the hydration hypothesis can readily be made. From equation 26,

$$\log K - \log K_{x_2} = d = \log [1 + (H)/(U)] \quad (28)$$

$(H)/(U)$ , the hydration equilibrium constant, may thus be evaluated from  $d$ , the divergence (caused by the existence of  $H$ ) of  $K_{x_2}$  at any temperature from the extrapolated value of  $K_U$  for that temperature. Now

$$d [\log (H)/(U)]/d(1/T) = -\frac{\Delta H_{hn}}{4.58} \quad (29)$$

If the hydration hypothesis is valid,  $\log [(H)/(U)]$  plotted against  $1/T$  should give straight lines, whose slopes correspond to reasonable values of

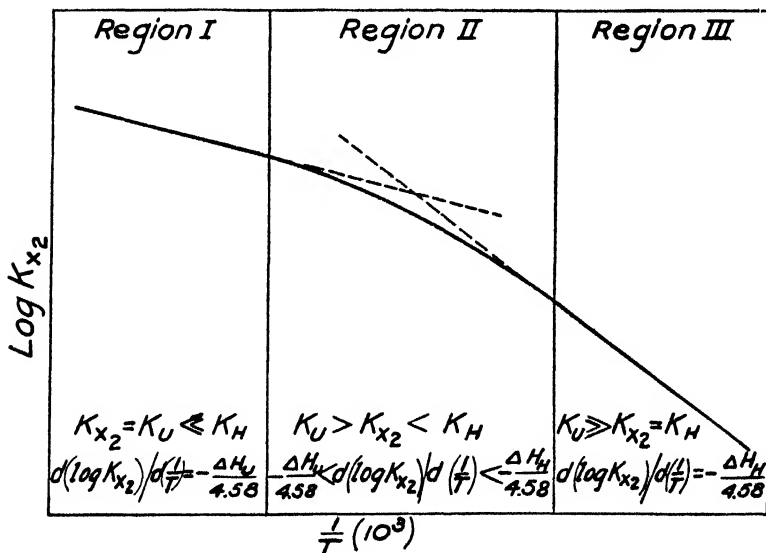


FIG. 6. Idealized effect of temperature change on an aqueous halogen equilibrium according to the hydration hypothesis.

the heat of hydration  $\Delta H_{hn}$ . The procedure for testing this hypothesis will be sketched for the data of figure 1. The equation for the best straight line through the experimental points at the higher temperatures was determined; the values of  $k'_2$  in this temperature region will be proportional to  $K_U = K_{x_2}$ . From this equation values of  $k'_2$  (calcd.), still proportional to  $K_U$ , were obtained for the lower temperatures, at which the experimental points fall on a curve. Here (region 2, figure 6)  $k'_2$  (measd.) is still propor-

tional to  $K_{X_2}$ ; so that  $d = \log k'_2$  (calcd.)  $- \log k'_2$  (measd.). Values of  $(H)/(U)$  for the various temperatures were obtained from these values of  $d$  by means of equation 28, and  $\log [(H)/(U)]$  was then plotted against  $1/T$ . The results (from both kinetic and equilibrium measurements) for the halogen hydrolyses are summarized in table 2 and plotted in figure 7. The results for the distribution equilibria are summarized in table 3 and plotted in figure 8.

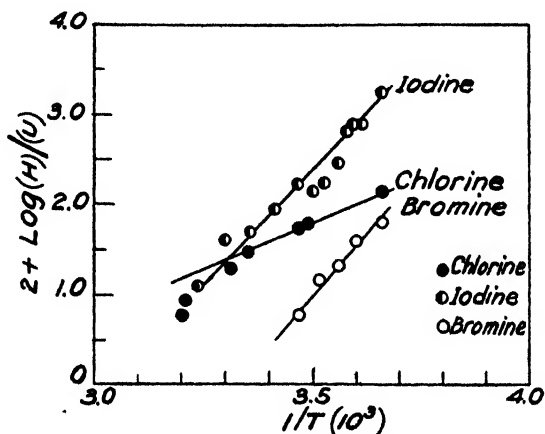


FIG. 7. Effects of temperature change on the hydration equilibria as computed from hydrolysis data for the halogens (cf. table 2).

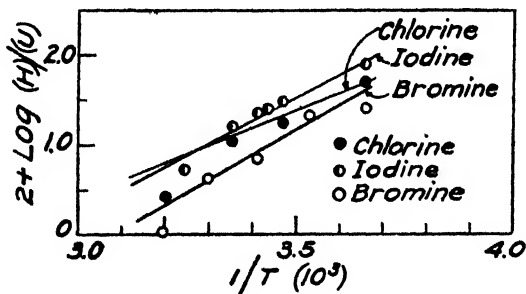


FIG. 8. Effects of temperature change on the hydration equilibria as computed from distribution data for the halogens (cf. table 3).

## V. DISCUSSION OF RESULTS

In deciding whether or not the extensive experimental evidence summarized in tables 2 and 3 proves the hydration hypothesis we have outlined, several things deserve consideration. First, the experimental errors associated with the measurements in region II are all reflected in figures 7 and 8, since no "smoothing out" of these results has been done. Second, the errors in  $d$  appear considerably enlarged in  $\log [(H)/(U)]$  at the higher





temperatures; a small error in  $k'_2$  (measd.) at 35.7°C. (table 2a) appears multiplied nearly tenfold in the hydration equilibrium constant. Third, if the limiting law in region I is in any case not exactly the straight line law we have assumed, then this will introduce an error in the calculated values used in determining  $d$ ; and such an error for a given point in region II will be larger the lower the temperature. Finally, because of the diversity of the experimental results, discussion of the errors peculiar to each set is scarcely feasible and will not be attempted.

When these considerations are given proper weight, it appears that the six sets of results plotted in figures 7 and 8 are sufficiently concordant to establish the hydration hypothesis as essentially correct. To this end, it should suffice to show that  $\log [(H)/(U)]$  for each set of results is a linear function of  $1/T$ ; examination of the figures leaves little doubt that this is true. (The data for reaction 2, table 2a, present the most convincing case, for here  $(H)/(U)$  varies nearly 150-fold.) To summarize: the evidence for the hydration hypothesis is all that could reasonably have been expected, although it is not completely free of inconsistencies.

Of these inconsistencies, the failure of reactions 10 and 12 to yield the same value of  $d$  where one reaction—the bromine hydrolysis—is involved, has already been discussed; those that remain are perhaps more serious. If our simple hydration hypothesis is to explain all the observed temperature coefficient anomalies, then we ought to obtain the same heat of hydration for a halogen no matter from what type of data this heat is deduced. Comparison of tables 2 and 3 shows that for chlorine the heats of hydration correspond to three sets of data to agree almost closely enough to require apology; but that for bromine and iodine large discrepancies exist. The source of these discrepancies may lie in the circumstance that the kinetic data (tables 2a and 2c; note, however, the agreement between tables 2c and 2d) and the equilibrium data (tables 3a and 3c) are not concordant; but what seems more likely, is that the anomalies cannot be completely "localized,"—i.e., that  $H^+$ ,  $X^-$ , and  $HXO$  (which are hydrated) are not in all cases simply interchangeable, as concerns our argument, with gaseous  $X_2$  (which is not). We may dismiss these unexplained inconsistencies with the statement that they do not seem sufficiently serious to threaten our main thesis, namely, that equilibria involving halogens in aqueous solution show anomalous temperature coefficients for which the simple hydration of the halogens is responsible.

The chlorine data, however, deserve further discussion. Figures 1 and 3 show that  $k'_2$  and  $k_2$  (which are proportional, respectively, to  $K_{X_2}$  for iodine and for bromine) can be satisfactorily represented (to within 1 or 2 per cent) by a limiting straight line at all temperatures above the intermediate region II. We have already mentioned that  $K_{Cl_2}$  does not behave thus,



and that Jakowkin expected it to become independent of  $T$  in the neighborhood of  $100^{\circ}\text{C}$ . Examination of figures 2 and 4b shows that  $K_{\text{Cl}_2}$  and  $D_{\text{Cl}_2}$  for the highest temperatures fall appreciably below the straight lines given in the figures. That this divergence almost certainly exceeds the experimental error follows from an examination of Jakowkin's work, and from a closer analysis of both sets of results. In the case of  $K_{\text{Cl}_2}$ , for example, the three points establishing the straight line conform to it very closely (the divergences in order of increasing temperatures are 0.3, 1.1, and 0.2 per cent); the next point falls 4 per cent below the line; while the last, at the highest temperature, is 19 per cent below. The corresponding departure for  $D_{\text{Cl}_2}$  is 9 per cent, an amount that may well be too small, since only two measurements are available to establish the straight line in figure 2a. We have now to extend our hydration hypothesis to explain this behavior.

In sketching this extension we shall assume that the limiting condition  $K_{\text{U}} = K_{\text{X}_2}$  (region I) is in fact fulfilled for chlorine at temperatures between  $40$  and  $60^{\circ}\text{C}$ .; if the close agreement of  $K_{\text{Cl}_2}$  for these temperatures with the straight line of figure 2 had not been obtained, we could have explained figure 2 on the assumption that this limiting condition is not reached even at the highest temperature. As matters stand, it seems more logical to assume that the temperature interval just above  $60^{\circ}\text{C}$ . represents a second transition region (analogous to region II) for chlorine, in which the hydrates,  $\text{U}$  and (say)  $\text{U}'$ , are both present in appreciable amounts. Obviously, we have insufficient data to test this assumption or to establish whether  $\Delta H_{\text{U}'}$  will be zero or even negative ( $\Delta H_{\text{U}}$ , of course, is positive). If  $\Delta H_{\text{U}'}$  is negative, heat will actually be liberated when  $\text{U}'$  hydrolyzes. This emphasizes how little significance may attach to the heat of hydrolysis of a halogen so long as the particular hydrate involved is left unspecified; this statement applied with equal force to all reactions of halogens in aqueous solutions and may be applicable to many others.

The question naturally arises as to what types of curves a hydration hypothesis like ours is capable of explaining. If  $\Delta H_{\text{U}'}$  for chlorine is negative, the complete  $\log K_{\text{Cl}_2}$  curve will be concave toward the  $1/T$  axis with its upper section nearly parallel thereto. (The logarithms of many dissociation constants give curves resembling this type (13)). It may be that any  $\log K$  versus  $1/T$  curves that are experimentally realizable and concave toward the  $1/T$  axis can be explained by assuming various hydrates of the reactants to exist in rapid equilibrium with each other. Whether such curves are concave or convex toward the  $1/T$  axis depends, of course, on the way in which the equilibrium constants are written. Our curves are concave because we have followed convention in placing the concentrations of the reactants in the denominator of the equilibrium constant expression;

were these concentrations written in the numerator of the equilibrium constant, all our curves would be convex. Also, the hydration of *resultants* (e.g.,  $\text{HXO}$  in the reaction  $\text{X}_2 + \text{H}_2\text{O} = \text{H}^+ + \text{X}^- + \text{HXO}$ ) could yield  $\log K$  versus  $1/T$  curves convex toward the  $1/T$  axis if the corresponding equilibrium constants are written in the conventional way. The situation becomes most complex when both reactants and resultants in a reaction at equilibrium exhibit a variable degree of hydration.

It is of interest, especially in connection with other equilibria that show anomalous temperature coefficients, to consider the application of the thermodynamic equation  $\partial\Delta H/\partial T = \Delta c_p$  to the type of data we have been discussing; for this purpose we shall return to the idealized figure 6. In the limiting regions I and III,  $\Delta c_p$  will be zero (or very small) since  $\Delta H_{\text{X}}$  does not vary appreciably; in the intermediate region II, however,  $\partial\Delta H_{\text{X}}/\partial T = \Delta c_p$  will reach a maximum (which may be very large) in the center, and decrease rapidly on either side as the limiting temperature regions are approached. Such behavior for a thermodynamic function indicates that a reformulation of the equilibrium involved may be necessary, which, of course, is exactly what we have done by means of our hydration hypothesis; our reformulation yielded constant heats of hydration (e.g., figure 7), and it did eliminate values of  $\Delta c_p$  that were unreasonably large (e.g., figure 1). Unfortunately, the experimental data themselves are scarcely accurate enough to warrant tabulation of the corresponding  $\partial\Delta H_{\text{X}}/\partial T = \Delta c_p$  values; if our hydration hypothesis is correct (as it appears to be) then such "heat capacity" values are altogether without real significance.

Another question of importance in connection with our hydration hypothesis will now be considered. This hypothesis has been advanced to explain temperature coefficient anomalies in an intermediate temperature region, the lower limit of which probably lies not far from  $0^\circ\text{C}$ .; we shall now discuss the position of this lower limit. Were the detailed experimental data sufficiently accurate, values of  $\partial Q/\partial T$ , or of  $\partial^2 Q/\partial T^2$ , might be used to establish at what temperature region II (figure 6) ends, and region III begins. Since the data do not appear to be sufficiently accurate, we must rely on the following cruder test. Examination of figure 6 and of the equations underlying it will show that the sum  $\Delta H_{\text{U}} + \Delta H_{\text{hn}}$  must equal  $\Delta H_{\text{H}}$ . For each set of data, the first two quantities are given in tables 2 and 3, and the heat term corresponding to the two lowest temperatures may be calculated from the experimental results for these temperatures. Now if this heat term is approximately equal to  $\Delta H_{\text{U}} + \Delta H_{\text{hn}}$ , then it is approximately equal also to  $\Delta H_{\text{H}}$ , and we may consequently assume that these experimental points lie very close to region III. Such comparisons have been made for all the data in tables 2 and 3, and, with the exception to be given, they have shown that region III is not realized above  $0^\circ\text{C}$ . (i.e.,

$\Delta H_U + \Delta H_{hn}$  is appreciably larger than the heat term corresponding to the two lowest temperatures. Reaction 2 is the exception.  $Q$  for this reaction increases from 24,800 cal. above 50°C. to 56,700 cal. between 3.5 and 0°C.;  $\Delta H_{hn}$  (table 2) is 22,800 cal. Now,  $Q$  should differ from  $\Delta H_U + \Delta H_{hn}$  and from  $\Delta H_H$  by approximately the same amount (namely, by the sum of the heat of dissociation of hypoiodous acid and the heat of activation of reaction 7), so that  $24,800 + 22,800 = 47,600$  should equal 56,700. This discrepancy of 9,000 cal., while large, is not alarming. The kinetic data for reaction 2 therefore indicate that region III occurs at a higher temperature for iodine than for bromine or chlorine.

#### VI. CONSEQUENCES AND APPLICATIONS OF THE HYDRATION HYPOTHESIS

##### *Halogen equilibria in non-aqueous solutions*

There seems to be no reason, *a priori*, why anomalous temperature coefficients for the halogens should be confined to aqueous solutions,—why such variations should not be characteristic of every solvent that contains an atom or a group of atoms with which the halogen can unite to form a solvate that becomes increasingly unstable as the temperature is increased. (Such solvates seem most easily formed with atoms—like oxygen, nitrogen, and sulfur—so combined in the solvent that they are capable of forming “onium” compounds.) It appears probable, therefore, that our hydration hypothesis can be expanded to a solvation hypothesis, and that the discovery for a solvent of a temperature coefficient like those under discussion is proof positive that a definite solvated compound exists.

##### *Colors of halogen solutions*

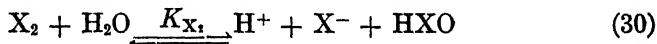
The bulk of the experimental material concerning the colors of halogen solutions deals with those of iodine, and we shall confine our discussion to this substance.

In connection with iodine solutions, two experimental facts (already mentioned above) are outstanding: Certain solvents give brown, others give violet solutions; it is sometimes possible to demonstrate a reversible color change from brown to violet by increasing the temperature. Beckmann's hypothesis that the brown color is evidence of solvation has received abundant support (15, 16, 33, 35); the quantitative study of the temperature effects (without which our understanding of these solutions can never be complete) is sometimes complicated by the occurrence of irreversible reactions between iodine and the solvent, and is difficult to carry out in detail (21). Getman (11) has recently published the results of an exceptionally careful quantitative investigation of light absorption by various iodine solutions, presumably at room temperature; measurements like his should be extended over temperature ranges within which any such solutions show

temperature coefficient anomalies, in order to discover whether the absorption curves reflect these peculiarities. Such a correlation of anomalous temperature coefficients due to solvation with the absorption spectra of halogen solutions would obviously contribute much to an understanding of these solutions.

### *Kinetics of halogen reactions*

The hypohalous acids and their anions are extraordinarily reactive and unstable substances, so that it is often impossible to isolate them for kinetic studies. Consequently, the principal evidence that these substances, and not the halogens themselves, are frequently the actual reactants when the latter act as oxidizing agents in aqueous solution has been the proof that the rate laws for such reactions are formally analogous to equation 4 or 11; i.e., the rates of these reactions are usually inversely proportional to some function of  $(H^+)$  and  $(X^-)$ , and this proportionality usually is taken to indicate that the hydrolysis equilibrium



is maintained and that  $HXO$  (or  $XO^-$ , but not  $X_2$ ) is actually involved in the rate-determining step. Rate-law evidence of this type, however, is not conclusive proof of mechanism (12); such proof is at hand only when it has been shown that  $HXO$  (or  $XO^-$ ) in the (virtual) absence of  $X_2$  does react with the reducing agent in question with the specific rate to be predicted from the reaction of this reducing agent with  $X_2$ . (In the case of reaction 10, for example, this specific rate,  $\kappa_2$ , equals  $k_2/K_{Br_2}$ ). Such conclusive proof of mechanism is usually difficult or impossible to obtain, so that another test of mechanism, to be applied in the cases of rate laws involving inverse  $(H^+)$  and  $(X^-)$  terms is highly desirable.

The experimental evidence, new and old, which has been presented above seems strong enough to warrant the conclusion that any  $\log K_{X_2}$  versus  $1/T$  plot must show a curvature concave toward the  $1/T$  axis. (Although this curvature finds a plausible explanation in our hydration hypothesis, its existence is empirically established and consequently independent of the validity of this hypothesis.) This curvature may now be utilized as a simple test of mechanism: If  $HXO$  or  $XO^-$  is the only halogen-containing substance involved in a rate-determining step, then the specific rate of the corresponding stoichiometric reaction must at all temperatures be proportional to  $K_{X_2}$  (cf. equations 2, 4, 5, 6, and 7; or equations 10, 11, 12, and 13) and must thus reflect this curvature in a  $\log k$  versus  $1/T$  plot. Since this argument has already been employed for reactions 2 and 10, it need not be elaborated; the fact that the specific rates of these reactions

meet this test increases our confidence in the mechanism we have outlined for them.

The value of this proposed test of mechanism cannot be assessed until it has been applied (as it will be) to other aqueous halogen reactions—in particular, to reactions whose mechanism has been “verified” in the sense that Makower and Liebhafsky (31) verified the mechanism of the bromine-oxalate reaction. If the test is valid, we must accept also the following corollary: If the rate of an aqueous halogen reaction is governed by the Arrhenius equation,  $HXO$  or  $XO^-$  cannot be the only halogen-containing substance involved in a rate-determining step, even though the rate law involves inverse ( $H^+$ ) and ( $X^-$ ) terms.

#### *Determination of equilibrium constants*

The statement has been made above that it will probably be impossible to obtain accurate direct measurements of  $K_{I_2}$ , the hydrolysis constant of iodine, near  $0^\circ C$ . If the data in figures 1 and 4a can be reconciled so that the curvature for a  $\log K_{I_2}$  versus  $1/T$  plot can be predicted either from the kinetic data (figure 1) or from the distribution data (figure 4a), then a knowledge of this curvature may be used in the calculation of  $K_{I_2}$  values for temperatures at which accurate direct measurements are impossible; for this calculation the results of such measurements must of course be available for some of the higher temperatures, at which they can be made. Further consideration of this problem will be postponed until the conductivity data obtained some time ago for aqueous iodine solutions (26) are prepared for publication; the problem is outlined here to emphasize the importance, not always appreciated, of correlating kinetic with equilibrium data, whenever this is possible.

#### VII. CONCLUSION

Experimental evidence from kinetic and from equilibrium measurements has been adduced to show that aqueous halogen solutions generally exhibit anomalous temperature coefficients. This evidence, obtained from many sources, seems conclusive; and it will consequently be necessary to take the existence of these anomalies into account whenever the effect of changing temperature on such a halogen solution is being considered.

The quantitative explanation which has been proposed for these anomalies is necessarily on less secure ground than are the experimental facts themselves. This explanation assumes that the temperature region in which the anomalies occur is the region in which the degree of hydration of the halogens is changing,—in which, therefore, two halogen species exist at comparable concentrations and in rapid equilibrium with each other. When the consequences of this hydration hypothesis have been experi-

mentally tested, and when its further applications have been explored, then its true value can be more readily assessed.

## REFERENCES

- (1) ANWAR-ULLAH: J. Chem. Soc. **1932**, 1176.
- (2) BAXTER AND GROSE: J. Am. Chem. Soc. **37**, 106 (1915).
- (3) BECKMANN: Z. physik. Chem. **5**, 76 (1890).
- (4) BECKMANN: Z. physik. Chem. **58**, 543 (1907).
- (5) BECKMANN AND STOCK: Z. physik. Chem. **17**, 107 (1895).
- (6) BRAY AND CONNOLLY: J. Am. Chem. Soc. **33**, 1485 (1911).
- (7) BRAY AND LIVINGSTON: J. Am. Chem. Soc. **45**, 125 (1923).
- (8) BRAY AND LIVINGSTON: J. Am. Chem. Soc. **50**, 1654 (1928).
- (9) D'ANS AND HÖFER: Z. angew. Chem. **47**, 71 (1934).
- (10) FÜRTH: Z. Elektrochem. **28**, 57 (1922).
- (11) GETMAN: J. Am. Chem. Soc. **50**, 2883 (1928).
- (12) HANTZSCH AND VAGT: Z. physik. Chem. **38**, 726 (1901).
- (13) HARNED AND EMBREE: J. Am. Chem. Soc. **56**, 1050 (1934).
- (14) HARRIS: J. Chem. Soc. **1932**, 582.
- (15) HILDEBRAND: Z. physik. Chem. **74**, 679 (1910), and references 3, 4, 5, and 12.
- (16) HILDEBRAND AND GLASCOCK: J. Am. Chem. Soc. **31**, 26 (1909).
- (17) International Critical Tables, Vol IV, p 31 McGraw-Hill Book Co., New York (1928).
- (18) JAKOWKIN: Z. physik. Chem. **29**, 613 (1899).
- (19) JONES AND BAECKSTROM: J. Am. Chem. Soc. **56**, 1517 (1934).
- (20) JONES AND HARTMANN: Trans. Am. Electrochem. Soc. **30**, 295 (1916).
- (21) KRÜSS AND THIELE: Z. anorg. Chem. **7**, 52 (1894), and references 37 and 35.
- (22) LIEBHAFSKY: Unpublished results (1931).
- (23) LIEBHAFSKY: J. Am. Chem. Soc. **54**, 1792 (1932). Paper I.
- (24) LIEBHAFSKY: J. Am. Chem. Soc. **54**, 3499 (1932). Papers II and III.
- (25) LIEBHAFSKY: Unpublished results (1932).
- (26) LIEBHAFSKY: J. Am. Chem. Soc. **56**, 2369 (1934). Paper IV.
- (27) LIEBHAFSKY: Unpublished results (1933).
- (28) LIEBHAFSKY: J. Am. Chem. Soc. **56**, 1500 (1934).
- (29) LIVINGSTON: J. Am. Chem. Soc. **48**, 53 (1926).
- (30) LIVINGSTON AND BRAY: J. Am. Chem. Soc. **45**, 2048 (1923).
- (31) MAKOWER AND LIEBHAFSKY: Trans. Faraday Soc. **39**, 597 (1933).
- (32) ROOZEBOOM: Z. physik. Chem. **2**, 449 (1888).
- (33) STRÖMHOLM: Z. physik. Chem. **44**, 721 (1903).
- (34) VILLARD: Compt. rend. **176**, 1516 (1923).
- (35) WAENTING: Z. physik. Chem. **68**, 513 (1909).
- (36) WALDEN: Z. physik. Chem. **43**, 415 (1903).
- (37) WIEDEMANN AND EBERT: Wied. Ann. **41**, 299 (1890).



# THE USE OF ISOTOPES IN ACID AND BASIC CATALYSIS

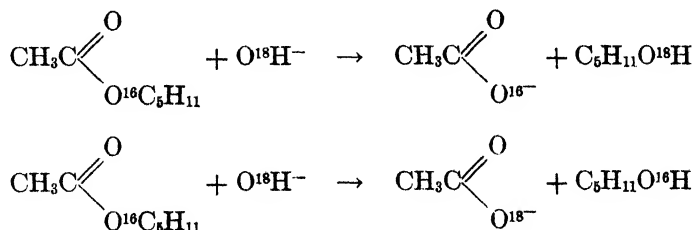
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*Received May 24, 1935*

In the study of reactions catalyzed by acids and bases there are two main problems,—the mechanism of the change in the molecule, and the function of the catalyst. The theory of these reactions advanced by Brønsted (2) has been amply verified by the work of Dawson (4), Hammett (7), Pedersen (18), and others, but an examination of the various reactions studied shows that we have not yet been able to solve completely the two problems stated. Thus for many reactions we cannot state what is the change that occurs in the reactant, nor can we explain why the relation between catalytic activity and dissociation constant is different for different reactions, and why some reactions appear to be catalyzed specifically by hydrogen or hydroxide ions. Fortunately, however, the questions which face us in this field are well defined, and it seems probable that we shall be able to answer at least some of them through the use of isotopes.

A very beautiful example of the value of isotopes in deciding the mechanism of a reaction is afforded by the work of Polanyi and Szabo (19), who used the isotope of oxygen,  $O^{18}$ , to distinguish between the alternative mechanisms for saponification of esters



They saponified amyl acetate in water containing 1 per cent of  $O^{18}$  and found that the oxygen in the alcohol produced was of normal isotopic composition. This proved that the saponification followed the second course, and also demonstrated that amyl alcohol does not ionize to  $\text{C}_5\text{H}_{11}^+$  and  $\text{OH}^-$ . The weight of earlier evidence, while strongly indicating the probability of both these ideas, was inadequate to establish them definitely.

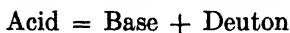


There are of course many other reactions that may be similarly investigated, but until  $O^{18}$  is available in considerably greater amounts the technique of such measurements will remain difficult.

The hydrogen isotope, deuterium, is of peculiar interest in acid and basic catalysis because it gives rise to a series of acids and bases distinct from but closely related to the ordinary protium series. Thus if we define the ordinary acids and bases by the scheme of Brönsted



we can define deutero-acids and bases by the scheme



As a consequence of the different masses and zero point energies of proto- and deutero-compounds, we find that the equilibria are shifted on proceeding from ordinary to heavy water and also that the velocities of prototropic and deuterotropic changes are different. In general, we can predict that the velocity of transfer of a proton will be greater than the velocity of transfer of a deuteron, and this enables us to distinguish between reactions catalyzed by acids and bases in general and reactions catalyzed specifically by hydrogen or hydroxide ions, which probably involve addition compounds.

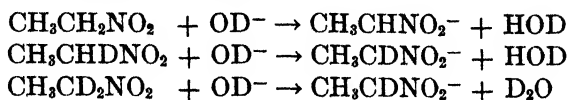
It is also possible to investigate the statistical factor, which was introduced by Brönsted and Pedersen (3) to take account of the probability of ionization of an acid with more than one ionizable hydrogen atom.

So far six reactions have been studied in heavy water, and in spite of the preliminary nature of the work certain general features are apparent. In table 1 the data for these reactions are summarized; the first column gives the reactant, the second the catalyst, and the third the ratio of the catalytic constants in  $H_2O$  and  $D_2O$ .

The result for nitramide is for a 6 per cent solution of heavy water in which the rate was 8 per cent less than in ordinary water. The hydrolysis of palmityl chloride was studied as a surface reaction. The three reactions which proceed more slowly in heavy water have all been shown to be subject to general acid or basic catalysis, whereas for the others such general catalysis has never been definitely established. In the case of the hydrolysis of ethyl acetate, Dawson (5) has claimed to have shown general catalysis, but his results are confused by salt effect and it now seems probable that the effective catalysts for this reaction are the hydrogen and hydroxide ions and, possibly, the water molecule, which is of course always one of the reacting molecules.

Probably the simplest of these reactions is the neutralization of nitro-

ethane, which has been shown by Pedersen (17) to involve simply the ionization of a hydrogen atom. The simplicity of the reaction makes it very suitable for the comparison of the rates of removal of protons and deuterons, and the fact that there are two ionizable hydrogen atoms makes possible the study of the successive reactions



The rate of this reaction in  $\text{H}_2\text{O}$  and the rates of the three stages in  $\text{D}_2\text{O}$  are given in table 2. It is apparent that the rate of removal of a proton is

TABLE 1  
*Reactions in  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$*

REACTANT	CATALYST	RATIO OF THE CATALYTIC CONSTANTS
Glucose (23) . . . . .	$\text{H}_2\text{O}$	3 8
	$\text{H}_2\text{O}^+$	1 33
Nitroethane (23) . . . . .	$\text{OH}^-$	6 0
Nitramide (10) . . . . .	$\text{H}_2\text{O}$	>1
Sucrose (6).. . . .	$\text{H}_2\text{O}^+$	0 5
Ethyl acetate (20, 24). . . . .	$\text{H}_2\text{O}^+$	0 67
	$\text{OH}^-$	0 75
Palmityl chloride (9) . . . . .	$\text{H}_2\text{O}$	1

TABLE 2  
*Neutralization of nitroethane (23)*

REACTANTS	RATE OF THE REACTION
$\text{CH}_3\text{CH}_2\text{NO}_2 + \text{OH}^-$ . . . . .	39
$\text{CH}_3\text{CH}_2\text{NO}_2 + \text{OD}^-$ . . . . .	60
$\text{CH}_3\text{CHDNO}_2 + \text{OD}^-$ . . . . .	36
$\text{CH}_3\text{CD}_2\text{NO}_2 + \text{OD}^-$ . . . . .	6

much greater than that of a deuteron, which of course is the reason that we are able to isolate the second stage in heavy water. The increase in rate of the first stage on going to heavy water may indicate that  $\text{OD}^-$  is a stronger base than  $\text{OH}^-$ .

The mutarotation of glucose has been studied by several workers. Pacsu (16) first showed that the rate in heavy water is much less than in ordinary water; later Moelwyn-Hughes, Klar, and Bonhoeffer (15) made a more detailed study, but their results are certainly in error since they failed to separate the effects of the various catalysts. The conclusions drawn by these authors as regards the activation energies and the mechanism of the

reaction are therefore open to doubt. The importance of separating the different reactions can be seen from figure 1, in which values of  $\log k$ , the reaction rate constant, have been plotted against the pH. Curve 1 represents the data for  $\text{H}_2\text{O}$  and curve 2 the data for  $\text{D}_2\text{O}$ ; the left branch of curve 2 referring to high pH's is unknown, and the probable limits are indicated by the dotted lines. The true catalytic constants for  $\text{D}_2\text{O}$  and

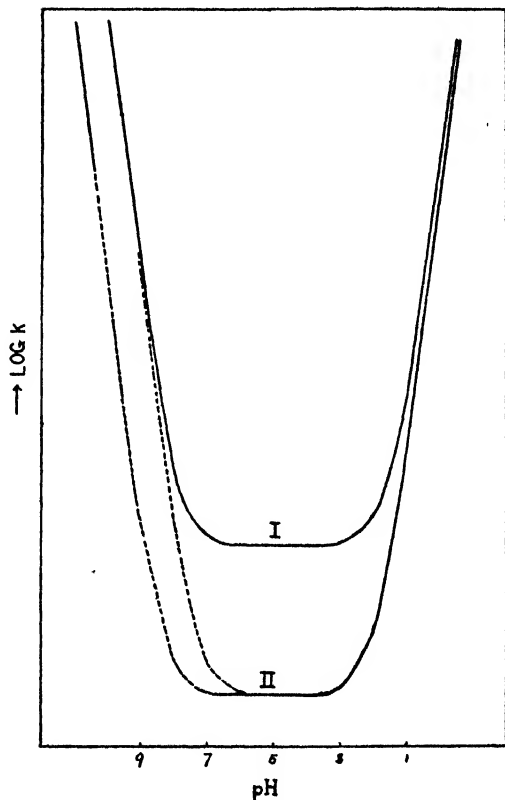
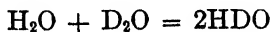


FIG. 1. Mutarotation of glucose

$\text{D}_3\text{O}^+$  are known only at  $23.3^\circ\text{C}$ .; these values have been employed in table 1.

The rate of mutarotation in mixtures of  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  has been measured by Hammill and La Mer (8), and their results are shown in figure 2. By combining their results with the equilibrium constant for the reaction (21)



these authors have calculated the catalytic constant of  $\text{HDO}$ , which they find to be 0.00498 compared with 0.01037 for  $\text{H}_2\text{O}$  and 0.00273 for  $\text{D}_2\text{O}$

at 25°C. They have also determined the catalytic constant of the hydrogen ion in  $\text{H}_2\text{O}$ - $\text{D}_2\text{O}$  mixtures and have found that the values vary linearly with the  $\text{D}_2\text{O}$  concentration. These results are of significance in connection with the statistical factor. Brönsted and Pedersen (3) suggested that if a polybasic acid  $\text{H}_n\text{A}$  acted as a catalyst its catalytic constant would be related to the dissociation constant by the equation:

$$k \left( \frac{p}{q} \cdot K \right)^z$$

where  $p$  is the number of protons that can dissociate, while  $q$  is the available points to which a proton can be attached. Pedersen (18) has recently

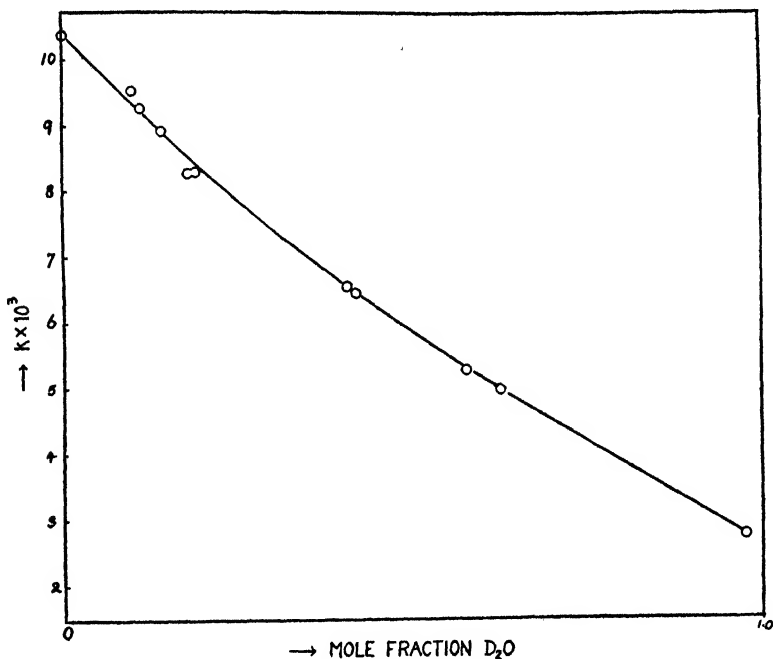


FIG. 2. Mutarotation of glucose

suggested that, if the protons are attached to a single atom,  $p$  and  $q$  are both unity however many protons there may be. On this theory the molecule  $\text{HDO}$  should have the same activity as  $\text{H}_2\text{O}$  or  $\text{D}_2\text{O}$ , whichever is the better catalyst, and similarly the ions  $\text{H}_2\text{DO}^+$  and  $\text{HD}_2\text{O}^+$  should be as effective as either  $\text{H}_3\text{O}^+$  or  $\text{D}_3\text{O}^+$ . We have seen that this is not true. Further evidence against this theory is given by the results on the neutralization of nitroethane, which showed that the rate of removal of a proton is reduced to one half when the number of protons is reduced from 2 to 1.

The measurements in heavy water showed that the mutarotation is strictly unimolecular, and hence proved that the exchange of hydrogen atoms between the sugar and water is very rapid.<sup>1</sup> This means that the rate-determining step is the reaction between a glucose ion and an acid or base. The change in constant between  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  shown in table 1 is markedly less for the hydrogen ion than for the water molecule; this may be explained on Pedersen's hypothesis that the water molecule acts as a basic catalyst. Alternatively, it may be due to changes in the acid strengths of these catalysts.

Moelwyn-Hughes and Bonhoeffer (13, 14) also investigated the inversion of cane sugar and found that in 90 per cent  $\text{D}_2\text{O}$  the catalytic effect of

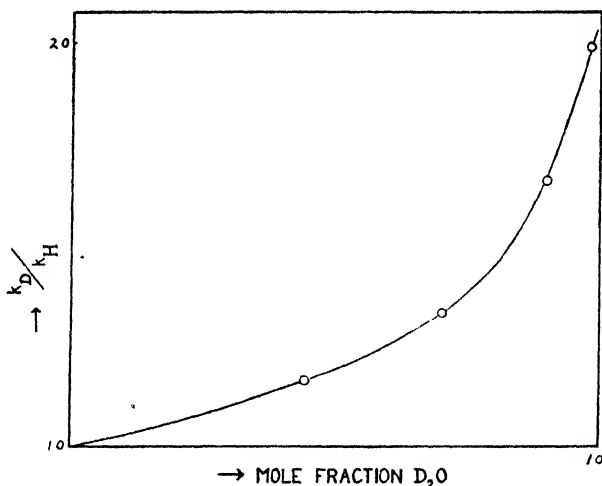
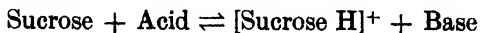


FIG. 3. Inversion of sucrose

hydrogen ions is 60 per cent greater than in  $\text{H}_2\text{O}$ . Gross, Suess, and Steiner (6) studied this reaction in  $\text{H}_2\text{O}$ - $\text{D}_2\text{O}$  mixtures, with the results shown in figure 3. The greater rate of reaction in  $\text{D}_2\text{O}$  suggests that there is an equilibrium of the type:



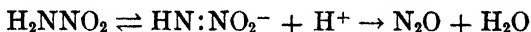
and the rate is determined by the decomposition of the sucrose ion. The form of the curve relating the catalytic constant of the hydrogen ion to the

<sup>1</sup> This is because the mutarotation of glucose is a reaction in which equilibrium is attained between  $\alpha$ - and  $\beta$ -glucose and the observed reaction constant is the sum of the constants for the forward and reverse reactions. If the exchange of deuterium for protium is not rapid, the nature of the glucose molecule will therefore be altering during the course of the reaction and the observed rate will not be unimolecular.

D<sub>2</sub>O concentration will be explicable in terms of the effects of the ions H<sub>2</sub>DO<sup>+</sup> and HD<sub>2</sub>O<sup>+</sup>.

The hydrolysis of esters is one of the classical reactions which have been extensively studied. Schwarz (20) examined the hydrolysis in heavy water in presence of hydrogen ions and found an increase of 50 per cent over the rate in ordinary water; this indicates that the reaction probably does not involve a keto-enol change. The hydrolysis by alkali studied by the change in the electrical conductivity also shows an increase, in this case of 33 per cent (24). From this increase we conclude that, if the reaction involves a prototropic change, this change must constitute the rate-determining step as in the neutralization of nitroethane. If, as for glucose, the exchange were instantaneous, there should be a decrease in rate. Actually it has been found that no exchange of hydrogen atoms occurs during the hydrolysis and consequently the reaction is not catalyzed by acids and bases in general.

The decomposition of nitramide is of special interest, as this was the first reaction for which general basic catalysis was established. Recently Pedersen (18) has suggested the following mechanism for the reaction:



Since this involves a dissociation followed by a basic catalysis, it is evident that the rate in heavy water may be considerably lower than in ordinary water; in fact, if the decrease in the dissociation is as great as for the acid examined by Lewis and Schutz (12), and, if the rate of deutron removal is less than the rate of removal of protons by the same factor as for nitroethane, the decomposition of nitramide should proceed in D<sub>2</sub>O at about one-twentieth of the rate in H<sub>2</sub>O.

Apart from the direct study of reaction rates, deuterium may be employed to investigate mechanisms by means of exchange of hydrogen atoms between the reactant and the catalyst. In general we may expect exchange to occur in solution and at room temperature whenever hydrogen atoms can be ionized; the conditions for exchange will therefore be similar to those for general acid and basic catalysis. The exchange of hydrogen atoms between water and acids and bases is of course inevitable and reveals nothing new, but the exchange between water and substances such as acetone, which exist in keto and enol forms, is significant. This exchange was first demonstrated by Bonhoeffer and Klar (1), who showed that, whereas the exchange proceeds slowly in neutral water, the rate is greater in acid and very rapid in alkali; these results precisely parallel the conditions for the iodination of acetone and confirm the suggestion of Lapworth (11) that the rate of iodination is simply that of the keto-enol change.

Some recent measurements show that exchange occurs with compounds

not usually suspected of having keto and enol forms; thus the anions of some carboxylic acids exchange their hydrogen atoms at a slow rate with water. The results of a few exchange reactions are given in table 3. These results do not necessarily represent equilibrium values, and consequently no conclusion can be drawn from them as to the distribution of deuterium atoms between the organic molecule and water. The exchange between the anions and water is of interest because of the marked differences in the rates; the malonate ion exchanges with great rapidity, while exchange with the formate ion is very slow. These differences are explicable partly on the basis of electrical effects, as in the Bjerrum theory of the dissociation

TABLE 3  
*Protium-deuterium exchange (22)*

SUBSTANCE	CONDITIONS	AMOUNT OF EXCHANGE
Formate .....	100 hrs. at 80°C.	8 3
Acetate.....	200 hrs. at 80°C.	85.0
Malonate.....	5 hrs. at 100°C.	100 0
Succinate .....	100 hrs. at 80°C.	69 0
Isatin....	12 hrs. at 100°C.	0 5 atom
Acetamide.....	1 hr. at 30°C.	2 atoms
Benzamide .....	10 mins. at 80°C.	1 26 atoms

TABLE 4  
*Dissociation constants in H<sub>2</sub>O and D<sub>2</sub>O*

ACID	BASE	DISSOCIATION CONSTANT IN H <sub>2</sub> O	DISSOCIATION CONSTANT IN D <sub>2</sub> O
H <sub>2</sub> O	H <sub>2</sub> O	55 5	55 4
H <sub>2</sub> O	OH <sup>-</sup>	$1.9 \times 10^{-16}$	$3.8 \times 10^{-17}$
CH <sub>3</sub> COOH	CH <sub>3</sub> COO <sup>-</sup>	$1.8 \times 10^{-5}$	$5 \times 10^{-6}$
CH <sub>2</sub> ClCOOH	CH <sub>2</sub> ClCOO <sup>-</sup>	$1.7 \times 10^{-5}$	$6 \times 10^{-6}$
NH <sub>4</sub> <sup>+</sup>	NH <sub>3</sub>	$5.5 \times 10^{-10}$	$2 \times 10^{-10}$

constants of dibasic acids, and partly by the enhanced effect of two carboxylic groups. The exchange between the acetate ion and water shows that it is possible that the bromination of acetic acid proceeds through the enol form as for acetone.

The dissociation constants of acids in heavy water are of obvious importance, and the available values are given in table 4. The values for acetic and chloroacetic acids and ammonia are those given by Lewis and Schutz (12), while the values for the water system are based on an electromotive force determination of  $K_w$  for D<sub>2</sub>O (25). An interesting deduction is that the acid strength of the water molecule compared with the hydrogen ion

is five times smaller in  $D_2O$  than in  $H_2O$ . In the further analysis of reaction rate studies in heavy water it will be essential to have the acid strengths of all the catalysts, since some of the change in catalytic activity between ordinary and heavy water may be directly related to the change in acid strength.

## REFERENCES

- (1) BONHOEFFER, K. F., AND KLAR, R.: *Naturwissenschaften* **22**, 45 (1934).
- (2) BRÖNSTED, J. N.: *Chem. Rev.* **5**, 45 (1928).
- (3) BRÖNSTED, J. N., AND PEDERSEN, K. J.: *Z. physik. Chem.* **108**, 185 (1924).
- (4) DAWSON, H. M., AND COWORKERS: *J. Chem. Soc.* **1926**, 2282, 2872 et al.
- (5) DAWSON, H. M., AND LOWSON, W.: *J. Chem. Soc.* **1927**, 2444.
- (6) GROSS, PH., SUESS, H., AND STEINER, H.: *Naturwissenschaften* **22**, 662 (1934).
- (7) HAMMETT, L. P.: *Chem. Rev.* **16**, 67 (1935)
- (8) HAMMILL, W. H., AND LA MER, V. K.: *J. Chem. Physics* **2**, 891 (1934).
- (9) HUGHES, A. H., YUDKIN, J., KEMP, I. AND RIDEAL, E. K.: *J. Chem. Soc.* **1934**, 1105.
- (10) LA MER, V. K.: Private communication.
- (11) LAPWORTH, A.: *J. Chem. Soc.* **85**, 30 (1904).
- (12) LEWIS, G. N., AND SCHUTZ, P. W.: *J. Am. Chem. Soc.* **56**, 1913 (1934).
- (13) MOELWYN-HUGHES, E. A.: *Z. physik. Chem.* **26B**, 272 (1934).
- (14) MOELWYN-HUGHES, E. A., AND BONHOEFFER, K. F.: *Naturwissenschaften* **22**, 174 (1934).
- (15) MOELWYN-HUGHES, E. A., KLAR, R., AND BONHOEFFER, K. F.: *Z. physik. Chem.* **169A**, 113 (1934).
- (16) PACSU, E.: *J. Am. Chem. Soc.* **55**, 5056 (1933); **56**, 745 (1934).
- (17) PEDERSEN, K. J.: *Kgl. Danske Videnskab. Selskab Math-fys. Medd.* **12**, No. 1 (1932).
- (18) PEDERSEN, K. J.: *Den almindelige Syre og Basekatalyse*. Thesis, Copenhagen, 1932.
- (19) POLANYI, M., AND SZABO, A. L. *Trans Faraday Soc.* **30**, 508 (1934).
- (20) SCHWARZ, K.: *Anz. Akad. Wiss. Wien.*, April 26, 1934.
- (21) TOPLEY, B., AND EYRING, H.: *J. Chem. Physics* **2**, 381 (1934).
- (22) TURKEVICH, J., AND WYNNE-JONES, W. F. K. Unpublished.
- (23) WYNNE-JONES, W. F. K.: *J. Chem. Physics* **2**, 381 (1934).
- (24) WYNNE-JONES, W. F. K.: Unpublished.
- (25) WYNNE-JONES, W. F. K.: Unpublished.





# SOME RELATIONS BETWEEN REACTION RATES AND EQUILIBRIUM CONSTANTS

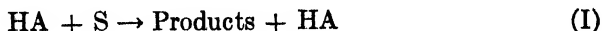
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*Received June 20, 1935*

The idea that there is some sort of relationship between the rate of a reaction and the equilibrium constant is one of the most persistently held and at the same time most emphatically denied concepts in chemical theory. Many organic chemists accept the idea without question and use it, frequently with considerable success, but practically every treatise on physical chemistry points out that such a relationship has no theoretical basis and that it is in fact contradicted in many familiar cases. The contradiction is however more apparent than real. It is certainly true that there is no universal and unique relation between the rate and the equilibrium of a reaction; it is equally true that there frequently is a relation between the rates and the equilibrium constants of a group of closely related reactions. It is the purpose of this paper to review the known examples of this kind of relationship, to point out the quantitative form which it assumes, and to state certain limitations to its application.

This quantitative form is the one which was first observed by Brönsted (9, 6) and his coworkers in the study of reactions which show general acid-base catalysis. These are second-order reactions between an acid catalyst HA and a substrate S



in which the acid is regenerated (and similar reactions in which the catalyst is a base). The rates of such reactions, for acid catalysts of a particular charge type, are related to the ionization constants of the acids by the equation

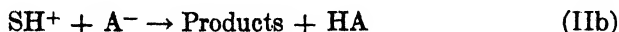
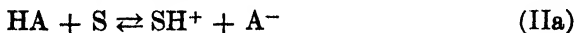
$$k = GK^x \quad (1a)$$

or 
$$\log k = x \log K + \log G \quad (1b)$$

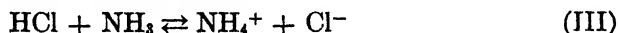
where  $k$  is the rate constant,  $K$  is the ionization constant, and  $G$  and  $x$  are constants.

This is obviously a relation between rates and equilibrium constants;

it is certainly not one between the rates and the equilibrium constants of the series of reactions I, whose equilibria are completely independent of the nature, the concentration, and even of the very presence of the catalyst HA. However it is overwhelmingly probable that this reaction takes place in steps, and Pedersen's (39, 40, 41) illuminating analysis suggests strongly that these steps are the following



Reaction IIb is presumably so rapid that the measured rate is that of IIa alone, which is nothing more nor less than an acid-base reaction like the reaction of ammonia and hydrogen chloride<sup>1</sup>



The equilibrium constants of the series of reactions of type IIa obtained by varying HA while keeping S constant are of thermodynamic necessity proportional to the ionization constants (measured in the same medium) of the series of acids HA. If this mechanism for the catalyzed reaction is correct, the relationship represented by equation I is indeed a relationship between the rates and the equilibrium constants of the same series of reactions, namely the series IIa. It is therefore strong evidence for the validity of the mechanism that the same quantitative relationship holds for numerous reactions which are clearly analogous to the step IIa and not at all to the total reaction I.

This appears especially well in the reaction of trimethylamine with a series of methyl esters of carboxylic acids (27). The general reaction



consists simply in the transfer of a positively charged methyl group from the ester to the base. Figure 1 shows a plot of the logarithms of the reaction rate constants,  $k$ , against the logarithms of the ionization constants,  $K$ , of the acids whose esters were used.<sup>2</sup> The straight line is of course a

<sup>1</sup> The widely held opinion that a reaction like IIa must be practically instantaneous is due to a quite unwarranted extrapolation from an experience which has been limited to relatively strong bases. The point has been well discussed by Pedersen (40, 41), but it may be added that Conant and Wheland (11) have actually observed simple acid-base reactions whose rates are measurable.

<sup>2</sup> This differs from the plots previously published by the inclusion of a point for salicylate from unpublished work of Pfluger, and in the fact that the ionization constants at 100°C. have been estimated for all the acids. In the case of phthalic and *p*-nitrobenzoic acids this estimate is based upon an application and extrapolation of the equation of Harned and Embree (28); in the case of lactic acid upon the behavior of other aliphatic acids.

graph of equation 1, which is seen to hold reasonably well, although by no means as exactly as it does in the catalytic reactions.

It would clearly be preferable to compare the rates of the series of reactions IV with the equilibrium constants of the same series of reactions, or, what would be entirely equivalent, with the equilibrium constants for the transfer of methyl ion from one acid radical to another.



Although it is entirely conceivable that these may be accessible to measurement they are not at present known. Lacking them the ionization con-

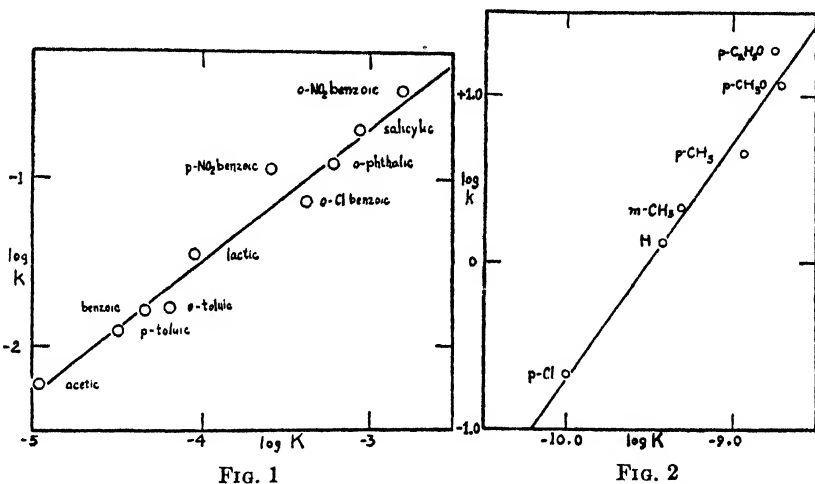
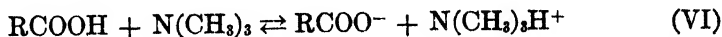


FIG. 1. Reaction of trimethylamine with methyl esters of carboxylic acids (Hammett and Pfluger).

FIG. 2. Reaction of dinitrochloronaphthalene with para and meta derivatives of aniline (van Opstall).

stants should be a good substitute, since they are proportional to the equilibrium constants of the series of reactions.



which differ from reactions IV, whose rates are measured only in the fact that a hydrogen ion is transferred instead of a methyl ion.<sup>3</sup>

<sup>3</sup> There is a certain difficulty involved in the fact that the ionization constants are functions of the solvent used. In the case of the catalytic reaction it has been demonstrated by Brönsted, Nicholson, and Delbanco (8) that much better agreement is obtained if the ionization constants are measured in the solvent in which the reaction rates are determined. The constants used in figure 1 are those measured in

The next four figures represent similar plots for four reaction series in which the base rather than the ester is varied. Here again the comparison is between the rates of a series of reactions in which a positively charged

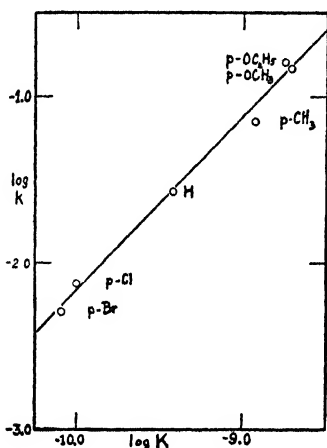


FIG. 3

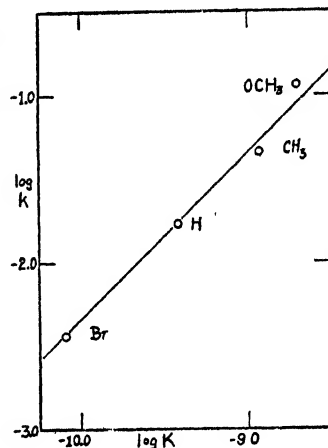


FIG. 4

FIG. 3. Reaction of methyl iodide with para derivatives of dimethylaniline (Davies and Lewis).

FIG. 4. Reaction of trinitrocresol methyl ether with para derivatives of dimethylaniline (Hertel and Dressel).

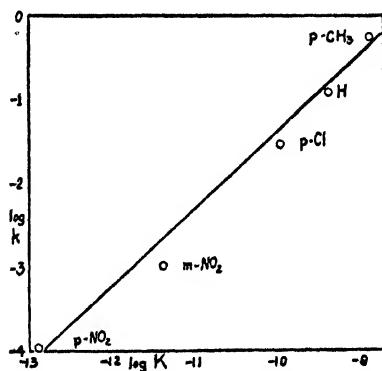


FIG. 5. Reaction of benzoyl chloride with para and meta derivatives of aniline (Grant and Hinshelwood).

water, but some preliminary measurements of Pfluger indicate that constants measured in methyl alcohol would give no better agreement. It is on the whole probable that the deviations due to the use of ionization constants instead of the equilibrium constants of the series of reactions IV are of about the same magnitude as the differences in relative strengths of a series of acids in different solvents.

organic group is transferred and the equilibrium constants of a series in which hydrogen ion is transferred. That is to say the  $K$ 's in these plots are ionization-constants of bases.<sup>4</sup>

Figure 2 is based upon the reaction rate data of van Opstall (44) for the series of reactions obtained by varying the group R in the equation

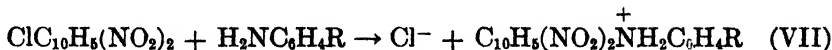


Figure 3 is based upon the data of Davies and Lewis (12) for the series

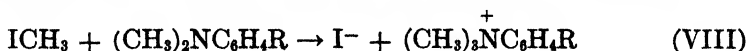
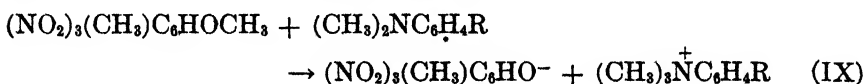
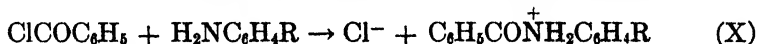


Figure 4 is based upon the data of Hertel and Dressel (29) for the series



and figure 5 upon that of Grant and Hinshelwood (19) for the series<sup>5</sup>



The agreement is about as good as in the case of the trimethylamine reaction (reaction IV), but only because a limitation was recognized which was not necessary in that case. These plots contain no points for ortho-substituted aniline derivatives, which react in fact at rates which are an order of magnitude slower than would be predicted from the strengths of the bases (43). The phenomenon is an obvious and indeed a familiar example of steric hindrance, for the organic chemist has long appreciated the fact that the reactions of ortho-substituted aniline derivatives are slower than they ought to be. The present correlation of rate and base strength seems to offer a definite criterion of the magnitude of the steric hindrance. It should also be noted that no correlation of rate and base strength is possible if comparisons are made between primary and tertiary amines, between aliphatic and aromatic amines, or even between dimethylaniline and diethylaniline derivatives.

A very similar situation appears in the case of the alkaline hydrolysis of esters. As was previously pointed out (27), there is no correlation whatsoever between the rates of hydrolysis of esters in general and the strengths

<sup>4</sup> In the case of the reactions represented in figures 3 and 4 they are the ionization constants of the bases  $\text{RC}_6\text{H}_4\text{NH}_2$  rather than those of the bases  $\text{RC}_6\text{H}_4\text{N}(\text{CH}_3)_3$ , because the base strengths of the dimethylaniline derivatives are not known.

<sup>5</sup> The ionization constants have been taken for the most part from the valuable compilations of Hall (21) and of Hall and Sprinkle (22). The value for *p*-nitroaniline is that of Hammett and Paul (26), and that for *m*-nitroaniline the one given by Farmer and Warth (17).

of the corresponding acids. But figure 6A shows that the correlation is quite satisfactory when *para*- and *meta*-substituted derivatives of benzoic acid alone are considered, and figure 6B shows that a similar correlation is obtained for ring-substituted derivatives of phenylacetic acid.<sup>6</sup> For a given acid strength the rate of hydrolysis of a phenylacetic ester is an order of magnitude faster than that of a benzoic ester. On the other hand the rates for *ortho*-substituted benzoic esters are so small that their representative points lie completely off this plot (30). This is of course a well-known example of steric hindrance.

It is an obvious generalization that correlations of this sort between the reaction rates and the equilibrium constants of a series of reactants will succeed only when the substitutions take place in a part of the molecule sufficiently removed from the point at which the reaction occurs. Unfortunately this "sufficient removal" is difficult of quantitative definition, and it varies from one reaction type to another. Thus an *ortho* substitution which exhibits a marked steric hindrance in the alkaline hydrolysis of esters has little if any effect of this sort in the reaction of the same esters with trimethylamine (27).

No such steric hindrance effects have so far been observed in acid or basic catalysis where the comparison is presumably between the rates and equilibrium constants of the same reaction series (IIa), even though some of the bases studied in the recent work of Brönsted, Nicholson, and Delbanco (8) on the nitramide reaction in *m*-cresol would be likely to exhibit the phenomenon if it exists.<sup>7</sup> It is therefore entirely possible that the steric hindrance effects would play a less important part in the reactions in which methyl or other organic groups are transferred if a direct comparison of rate and equilibrium constants in these reactions were to be made. In other words, it may be that the steric hindrances represent as much a failure of the relationship between the equilibrium constants of the methyl and hydrogen reactions as they do a failure of the relationship between rate and equilibrium constant in the methyl reaction.

The reactions thus far considered are of the type



This may be called a substitution in the sense that the radical C substitutes for the radical A in its combination with B. In the basic catalysis and in reactions VII, VIII, IX, and X the group C is varied to obtain the series of reactions for which a correlation is obtained. In the acid catalysis and in the trimethylamine reaction (reaction IV) a similar correlation is obtained

<sup>6</sup> The rate constants are taken from the valuable papers of Kindler (30).

<sup>7</sup> This is especially true of the use of *o*-chloroaniline and of the direct comparison of aniline, monomethylaniline, and dimethylaniline.

for changes in the nature of the group A. Since the mechanism of ester hydrolysis is<sup>8</sup>



this series of reactions is of the third possible type, that obtained by variation of the B component. Such a variation does not produce (31) and would not be expected to produce any large changes in equilibrium constants, because the affinity for  $\text{HO}^-$  and for  $\text{C}_2\text{H}_5\text{O}^-$  must be similarly affected by the substitution. There are, however, large changes in reaction rate and these correlate satisfactorily, as figure 6 shows, with the

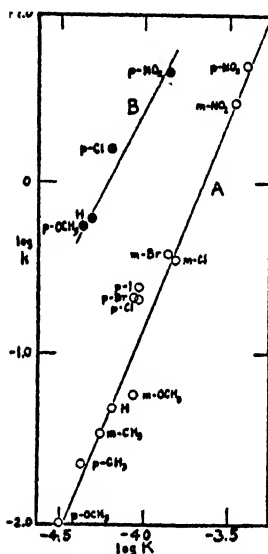
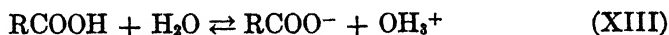


FIG. 6. Alkaline hydrolysis of (A) para and meta derivatives of ethyl benzoate and (B) para derivatives of ethyl phenylacetate (Kindler).

equilibrium constants of a quite different series of reactions, those of ionization. This result is a rather surprising one, because the ionization reaction



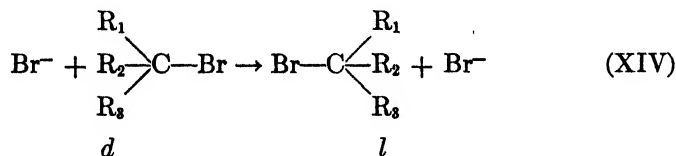
involves the separation of an anion  $\text{RCOO}^-$ , while the ester hydrolysis involves the transfer from one group to another of a positively charged

<sup>8</sup> This follows from a number of considerations (27), but most clearly from the recent work of Polanyi and Szabo (42), in which the bridge oxygen was demonstrated to go with the alkyl group by carrying out the reaction in water containing an increased concentration of  $\text{O}^{18}$ .



acyl group,  $\text{RCO}^+$ . The bonds broken are of a very different nature, but the experiment shows that their strengths are similarly affected by changes in the group R, provided these changes occur at a sufficient distance from the carboxyl group.

The same situation appears even more strikingly in the case of racemization reactions. These consist, as has been convincingly shown by Polanyi (3, 35) and by Olson (36, 37, 38), in a substitution of one group on an asymmetric carbon atom by another completely identical group, but with accompanying inversion of the configuration of the asymmetric carbon.



While the equilibrium constant is necessarily unity for all such reactions, the rates vary greatly with changes in the B component or in the identical

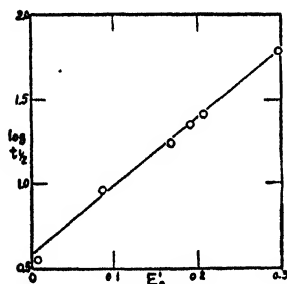


FIG. 7

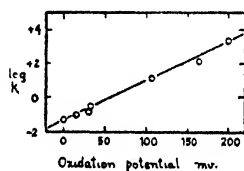


FIG. 8

FIG. 7. Autooxidation of reduced indicator dyes (Barron)

FIG. 8. Reaction of a series of quinones with dihydrophenyllutidinedicarboxylic ester (Dimroth).

A and C components. There is therefore no correlation whatsoever between the rates and the equilibria of reactions of type XIV. It is, however, to be expected that the racemization rates should correlate with the rates of other reactions involving the same groups or perhaps, as in the case of ester hydrolysis, with suitable equilibrium constants.

Equation 1 has also been found to apply to reactions of a different type, to oxidation-reduction reactions. In fact, the first observation of this relationship in any reaction except an acid or basic catalysis seems to be that of Barron (2). He found a linear relation between the logarithms of  $t_{\frac{1}{2}}$ , the time required for 50 per cent oxidation by oxygen of various reduced

dyes of the oxidation indicator type, and the molar oxidation potentials,  $E'_0$ , of the dyes. Since the latter are proportional to the logarithms of the equilibrium constants of the oxidation-reduction reactions, this relationship is equivalent to equation 1. Figure 7 is taken from his work.

Dimroth (14) in an extensive series of investigations found that the same relation holds for the reactions of a series of quinone derivatives with an organic reducing agent. An example is given in figure 8, the reducing agent being dihydrophenyllutidinedicarboxylic ester. The agreement is equally good with other reducing agents, and also for the oxidation of a series of derivatives of hydroquinone by hexanitroazobenzene.

Chow (10) has found that the catalytic effect of such oxidant-reductant systems as ferricyanide-ferrocyanide upon the rate of autoxidation of linseed oil is similarly determined by the oxidation potential of the catalyst system.

Finally Frumkin (18) has made an interesting suggestion which relates the problem of the current-voltage relation in electrochemical reactions to the present one. It is known (4, 5), for instance, that the rate of hydrogen evolution on an electrode, measured of course by the current  $I$ , is related to the polarization potential  $\Delta E$  by the equation<sup>9</sup>

$$RT \ln I = \frac{1}{2} F \Delta E + \text{const.} \quad (2)$$

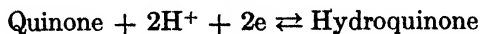
Frumkin suggests that increasing the negative polarizing potential increases the affinity of the electrode for hydrogen ion and is equivalent to the substitution in an acid-base reaction of a stronger base for a weaker one. The change in ionization constant  $K$  of the hypothetical base is given by

$$RT \ln K = -F \Delta E + \text{const.} \quad (3)$$

so that the polarization equation becomes

$$\ln I = -\frac{1}{2} \ln K + \text{const.} \quad (4)$$

The  $\frac{1}{2}$  coefficient in this equation is equivalent to the coefficient  $x$  which appears in equation 1. The same factor,  $\frac{1}{2}$ , is found in the polarization equation for the electrochemical reaction (24)



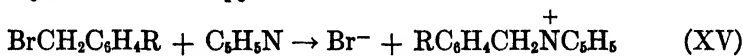
and also in the rate equations for some reactions in which the equivalent of a polarization is obtained by varying the concentration of a metal in an amalgam (7, 13, 18, 25).

<sup>9</sup> This is true only at relatively high overvoltages, where the rate-determining process seems to be the reaction  $\text{H} + \text{e} \rightarrow \text{H}$  alone, and not at lower overvoltages where the reaction  $2\text{H} \rightleftharpoons \text{H}_2$  determines the rate (23).

There are a number of corollaries to the existence of the relationships represented by equation 1. One of the most obvious is the conclusion that the rate constants  $k_1$  of one series of reactions should be related to the constants  $k_2$  of another similar series by the equation

$$\log k_1 = x \log k_2 + \text{const.} \quad (5)$$

Figure 9 shows the application of this expectation to the work of Baker (1) on substituted benzyl halides.  $k_1$  is the rate of reaction of various derivatives of benzyl bromide with pyridine.



$k_2$  is the rate of the hydrolysis of the same benzyl bromide derivatives.



A correlation of this sort is an argument in favor of a fundamental similarity in the mechanisms of the reactions compared, and may therefore

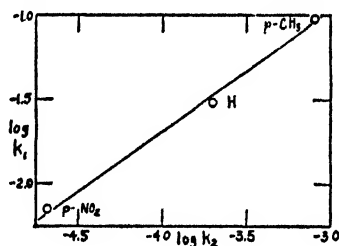
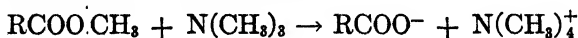
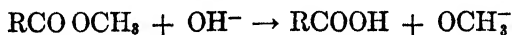


FIG. 9. Reaction of derivatives of benzyl bromide with pyridine and with water (Baker).

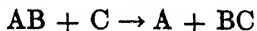
be of considerable assistance in the diagnosis of reaction mechanisms. Conversely, a failure of such a correlation is evidence of some difference in mechanism (27). Such an argument has been used in the comparison of the mechanisms of the reaction of an ester with trimethylamine and with hydroxyl ion. The trimethylamine reaction necessarily splits the ester on the alcohol side of the ether oxygen.



From the fact that steric hindrance due to ortho substitution is so much more significant in the hydrolysis reaction than in the reaction with trimethylamine, it was concluded that the hydrolysis takes place at a point in the molecule nearer the ortho substituent, and probably involves a split on the acid side of the ether oxygen.<sup>8</sup>



It is an important feature of the material cited in this paper that reaction rates in the type reaction



have been found to depend upon the equilibrium constant and hence upon the standard free energies of dissociation of both AB and BC. In the acid catalysis and in reaction IV the rate is dependent upon the free energy of the bond being broken (AB); in the basic catalysis and in reactions VII, VIII, IX, and X, it depends upon the free energy of the bond being formed (BC). There seems to be only one mechanism which leads simply and clearly to the expectation that the rate of a substitution reaction should be affected both by the bond being broken and by that being formed. This is the one proposed by London (32), Polanyi (3, 33, 34, 35), Eyring (16), and Olson (36, 37, 38), in which the combination of C with B proceeds simultaneously with the dissociation of A from B, and in which the height of the potential energy peak which must be overcome at the expense of the mutual kinetic energy of AB and C if reaction is to occur is a function among other things of the energies of dissociation of both AB and BC.

Unfortunately it has not so far been possible to develop this rather vague relation between the height of the potential energy peak and the dissociation energies into the definite and simple relation between the reaction rate and the free energy of dissociation which appears in equation 1. The recent attempt in this direction of Ogg and Polanyi (34), like the earlier attempts of Gurney (20) and of Erdey-Gruz and Volmer (15) to derive the polarization equation (2), leads only to a parallelism between rate and equilibrium, and is entirely incompetent to predict the exact linearity of the relation shown in equation 1b. This relation is in fact too widespread in its applicability and too exact in the more favorable cases for a test of its validity to be accounted for as the first-order approximation of a complicated function.

#### REFERENCES

- (1) BAKER: J. Chem. Soc. **1934**, 987.
- (2) BARRON: J. Biol. Chem. **97**, 287 (1932).
- (3) BERGMANN, POLANYI, AND SZABO: Z. physik. Chem. **20B**, 161 (1933).
- (4) BOWDEN: Trans. Faraday Soc. **24**, 473 (1928).
- (5) BOWDEN: Proc. Roy. Soc. London **126A**, 107 (1929).
- (6) BRÖNSTED: Chem. Rev. **5**, 231 (1928).
- (7) BRÖNSTED AND KANE: J. Am. Chem. Soc. **53**, 3624 (1931).
- (8) BRÖNSTED, NICHOLSON, AND DELBANCO: Z. physik. Chem. **169A**, 379 (1934).
- (9) BRÖNSTED AND PEDERSEN: Z. physik. Chem. **108**, 185 (1924).
- (10) CHOW: J. Am. Chem. Soc. **56**, 894 (1934).
- (11) CONANT AND WHELAND: J. Am. Chem. Soc. **54**, 1212 (1932).
- (12) DAVIES AND LEWIS: J. Chem. Soc. **1934**, 1599.
- (13) DEYRUP: J. Am. Chem. Soc. **56**, 2594 (1934).

- (14) DIMROTH: *Z. angew. Chem.* **46**, 571 (1933).
- (15) ERDEY-GRUZ AND VOLMER: *Z. physik. Chem.* **150A**, 203 (1930).
- (16) EYRING AND POLANYI: *Z. physik. Chem.* **12B**, 279 (1931).
- (17) FARMER AND WARTH: *J. Chem. Soc.* **85**, 1713 (1904).
- (18) FRUMKIN: *Z. physik. Chem.* **160A**, 116 (1932).
- (19) GRANT AND HINSHELWOOD: *J. Chem. Soc.* **1933**, 1351.
- (20) GURNEY: *Proc. Roy. Soc. London* **134A**, 137 (1931); **136A**, 378 (1932).
- (21) HALL: *J. Am. Chem. Soc.* **52**, 5115 (1930).
- (22) HALL AND SPRINKLE: *J. Am. Chem. Soc.* **54**, 3469 (1932).
- (23) HAMMETT: *Trans. Faraday Soc.* **29**, 770 (1933).
- (24) HAMMETT: *J. Am. Chem. Soc.* **46**, 7 (1924).
- (25) HAMMETT AND LORCH: *J. Am. Chem. Soc.* **54**, 2128 (1932).
- (26) HAMMETT AND PAUL: *J. Am. Chem. Soc.* **56**, 827 (1932).
- (27) HAMMETT AND PFLUGER: *J. Am. Chem. Soc.* **55**, 4079 (1933).
- (28) HARNED AND EMBREE: *J. Am. Chem. Soc.* **56**, 1050 (1934).
- (29) HERTEL AND DRESSEL: *Z. physik. Chem.* **23B**, 281 (1934).
- (30) KINDLER: *Ann.* **450**, 1 (1926); **452**, 90 (1927); **464**, 278 (1928).
- (31) LICHTY: *Am. Chem. J.* **18**, 590 (1896).
- (32) LONDON: *Z. Elektrochem* **35**, 552 (1929).
- (33) MEER AND POLANYI: *Z. physik. Chem.* **19B**, 164 (1932).
- (34) OGG AND POLANYI: *Trans. Faraday Soc.* **31**, 604 (1935).
- (35) OGG, POLANYI, AND WERNER: *Chemistry and Industry* **1934**, 614.
- (36) OLSON: *J. Chem. Physics* **1**, 418 (1933).
- (37) OLSON AND LONG: *J. Am. Chem. Soc.* **56**, 1294 (1934).
- (38) OLSON AND VOGEL: *J. Am. Chem. Soc.* **56**, 1690 (1934).
- (39) PEDERSEN: *J. Am. Chem. Soc.* **53**, 18 (1931).
- (40) PEDERSEN: *Den almindelige Syre- og Basekatalyse*. Thesis, Copenhagen, 1932.
- (41) PEDERSEN: *J. Phys. Chem.* **38**, 581 (1934).
- (42) POLANYI AND SZABO: *Trans. Faraday Soc.* **30**, 508 (1934).
- (43) THOMAS: *J. Chem. Soc.* **103**, 594 (1913).
- (44) VAN OPSTALL: *Rec. trav. chim.* **52**, 901 (1933).

# THE MECHANISM OF SOME IMPORTANT ORGANIC REACTIONS

## THE DISSOCIATION OF CARBON BONDS<sup>1</sup>

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The dissociation of carbon bonds is one of the most important reactions in organic chemistry. The cracking process and the scission of sugar are examples which reveal not only its importance in industry, but also in the whole life process itself.

### THE SCISSION OF A HOMOPOLAR BINDING

The rupture of carbon bonds is a process of dissociation; a homopolar bond between two carbon atoms is broken and two molecules are formed from one.

A bond is heteropolar if the residues which are connected by it are ions, and homopolar if they are not; in the first case the energy of binding is due to Coulomb attraction, in the second to the resonance energy of two electrons of different spin. The molecules of simple gases such as hydrogen and chlorine and those of the enormous number of organic compounds are held together by homopolar bindings.

In the first paper (32) on the mechanism of heterogeneous catalytic organic reactions we discussed catalytic hydrogenation, a reaction in which the atoms of the hydrogen molecule are attached to a double bond:



In this case we also have a process of splitting off homopolar bonds; the binding between the two hydrogen atoms and one of the double bonds must be loosened to give ethane as end product.

<sup>1</sup> This is the second of a series of three papers; for the first see reference 32.

We have seen that the mechanism of this process is quite different with different catalysts and have found that there are two classes of catalysts. The first consists of the higher elements of the alkali group and the elements of the alkaline earths; these elements have large atomic and ionic volumes and small work functions. The second consists of transition elements, e.g., the elements of the iron and platinum group, with small atomic and ionic volumes and relatively large work functions.

With catalysts of the first class hydrogen is activated by forming primarily negative ions:



With catalysts of the second class primarily positive ions of hydrogen, especially protons, are formed:



The third possibility, that primarily the hydrogen molecule is split into two atoms without adding or subtracting electrons,



seems not to be effected in catalytic hydrogenation, which occurs in metallic solution. But in the reactions in which carbon bonds are broken, normally uncharged groups or residues are formed as in equation 3.

To investigate reactions of this type, we must first consider thermal dissociations in the gas space, in which wall-effects do not occur. The cracking of hydrocarbons in vessels of quartz or Pyrex glass is a monomolecular and homogeneous reaction, as Pease and Durgan (24) have shown. According to the definition of van't Hoff, in a monomolecular reaction a molecule is split according to the equation:



First the molecule of the hydrocarbon must take up internal energy in order that the work of dissociation can be done. This is effected by an inelastic impact. The process of dissociation, as for instance the elementary process of the cracking reaction, is therefore divided into three phases: (1) the inelastic impact, (2) the dissociation into two particles, and (3) the subsequent reactions.

In the following, we consider only the last two phases of the process.<sup>2</sup>

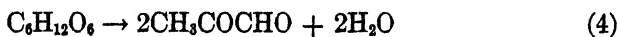
<sup>2</sup> The first phase has been discussed by the author (Ann. Physik [5] 21, 241-67, 268-73 (1934)).

We begin with the scission of the sugar molecule *in dilute aqueous solution* a process which is comparable to a reaction in the gaseous state.

*A. The scission of the sugar molecule*

A large fraction of enzymatic reactions in the living cell consists of reactions in which homopolar bonds from carbon to carbon or to other atoms are split. In the process of fermentation by the enzymes of yeast, such as zymase, bonds between carbon atoms are broken. The esterases such as lipase, the chlorophyllases, the carbohydrases such as saccharase, maltase, and emulsin loosen the bond between carbon and oxygen. The proteases such as pepsin, trypsin, and papain, the amidases such as histocyme, arginase, and urease, loosen the bond between carbon and nitrogen. In many cases, as in the processes of fermentation and of digestion, for instance, these reactions are not reversible and lead to a diminution of the molecular weight.

Neuberg and his coworkers have found (19) that the enzymatic scission of glucose follows the equation



First the glucose is split into two molecules of methylglyoxal, with three carbon atoms in the molecule, and therefore the rupture of carbon bonds takes place in the middle of the carbon chain. The molecule of methylglyoxal is then converted into alcohol and carbon dioxide.

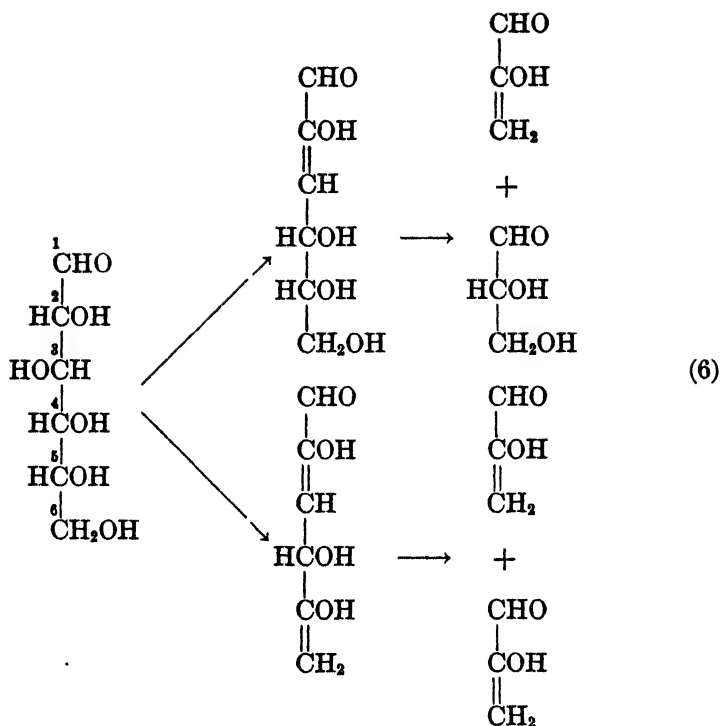
The scission of the molecule of glucose in the organism produces lactic acid, also a compound with three carbon atoms in the molecule:



The conversion of glucose in blood into lactic acid is produced by the leucocytes, which cover the lack in energy for the life process by this scission (1); in carcinomas the production of lactic acid from blood sugar is a typical process of the cancer cells, as Warburg has shown (39, 40); finally the oxidative combustion of the lactic acid produced by glucolysis delivers the energy to the working muscle, as Meyerhof has shown (7).

Neuberg formulates the scission of glucose (23) in the following manner, supposing that first the oxydic bonds are broken and a free aldehyde group is formed, a process called oxycyclodesmotropism by Jacobson.





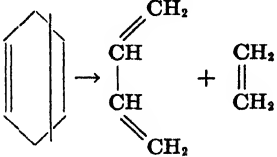
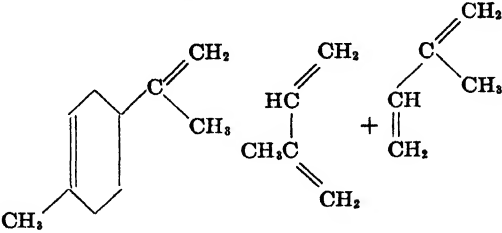
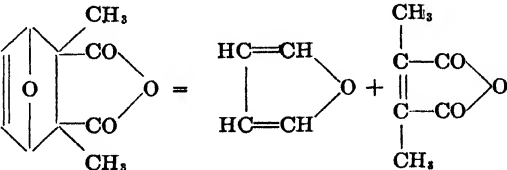
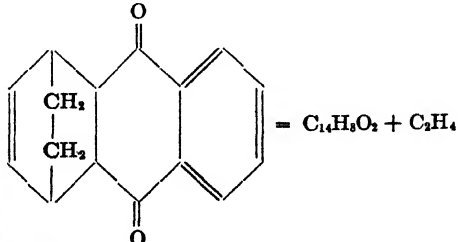
This formulation cannot be right. As I have shown (29), the double bond between two carbon atoms strengthens the following single carbon bond and weakens the next following; this alternation of strong and weak single carbon bonds goes through the whole carbon chain with decreasing energy (double bond rule). Examples for this rule are given in table 1. Therefore, counting from the double bond as one, the next single carbon bond<sup>3</sup> 2 is strengthened, the following bond 3 is weakened. Bond 2, beside the double bond, is never broken within wide limits of temperature. In the formulas of Neuberg the double bond lies by the side of the bond to be dissociated; here a rupture is impossible.

The scission of glucose into two parts each with three carbon atoms in the molecule is not only effected by the enzymatic bodies of the yeast and the ferments of the cell, but also by hydroxyl ions. These are also able to split glucose into methylglyoxal, although this homogeneous reaction does not proceed with the same good yield and the same uniformity as the micro-heterogeneous one that is produced by the enzymes of yeast.

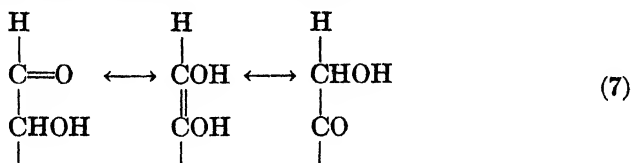
Nef (17) has made a special study of the reaction of hydroxyl ions in

<sup>3</sup> Bond 2 is the bond between the carbon atoms 2 and 3; bond 3 that between carbon atoms 3 and 4, etc.

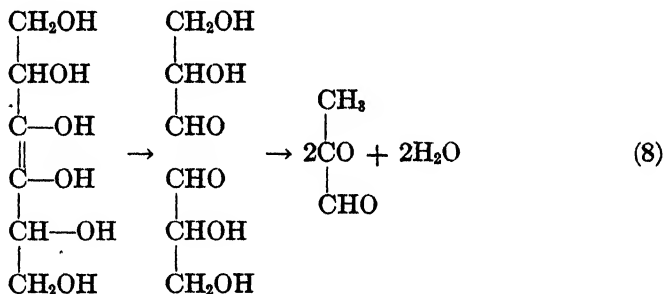
TABLE 1  
Examples for the double bond rule

COMPOUND	RESULT	SCISSION RELATIVE TO THE DOUBLE BOND (=1) IN	AUTHOR
$\alpha$ -Butylene .	$\text{CH}_2=\text{CH}\cdot\text{CH}_2\cdot\text{CH}_3 \begin{cases} \nearrow \text{CH}_2:\text{CH}\cdot\text{CH}:\text{CH}_2 + \text{H}_2 \\ \searrow \text{CH}_2:\text{CH}\cdot\text{CH}_3 + \text{CH}_4 \end{cases}$	3	Calin- gaert (44)
Natural rubber ...	$+ \text{CH}_2-\underset{\text{CH}_3}{\text{C}}=\text{CH}-\text{CH}_2 + \text{CH}_2-\underset{\text{CH}_3}{\text{C}}=\text{CH}-\text{CH}_2 +$	3	Williams (45)
Ricinoleic acid....	$\text{CH}_3-[\text{CH}_2]_6-\underset{\text{OH}}{\text{CH}}-\text{CH}_2-\text{CH} \longrightarrow \begin{matrix} \text{CH} \\ \parallel \\ \text{CH}-[\text{CH}_2]_7\text{COOH} \end{matrix}$ <p style="text-align: center;">Heptaldehyde                      Undecylenic acid</p>	3	Krafft (46)
Tetrahydro- benzene .		3	Schmidt (47)
Dipentene .		3	Staudin- ger (48)
Dehydrated canthari- dine.....		3	v. Bruch- hausen and Bersch (49)
Endo- ethylene dihydro- anthraqui- none .....		3	Diels and Alder (50)

alkaline aqueous solutions and glucose. It is well known that hydroxyl ions isomerize the aldehyde and keto group into enols; e.g., the esters of acetoacetic acid, which consist chiefly of the keto form in liquid state, are enolized by alkali. Therefore, in the hexoses, we get 1,2-dienols from the aldehyde or keto group according to the following scheme:

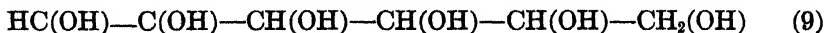


As the 2-ketose can also give a 2,3-dienol, which can be produced by a 3-ketose, it is apparent that the double bond can thus run through the whole sugar molecule. Indeed Nef assumes this sequence of reactions and believes that the 3,4-dienol is the intermediate product of the scission of sugar with formation of glyceric aldehyde, which then easily produces methylglyoxal.



The 1,2-dienols, according to Nef, are broken into chains of five carbon atoms; the 2,3-dienols into chains of four carbon atoms. This explanation seems very improbable. The 3,4-dienol is, according to Nef, the product of a series of changes of the 1,2- and 2,3-dienol; it is not possible to understand why scission would take place only at the end of this series and not at every intermediate stage. A quantitative yield with compounds of three carbon atoms, such as we get in the scission of sugar by enzymes in the process of fermentation, is completely incomprehensible.

The double bond rule gives another explanation, which is more probable. Even the 1,2-dienol, the first product of conversion of glucose, can be broken in the middle because the bond between the carbon atoms 3 and 4 is weakened. Therefore the reaction goes on as follows: the molecule,



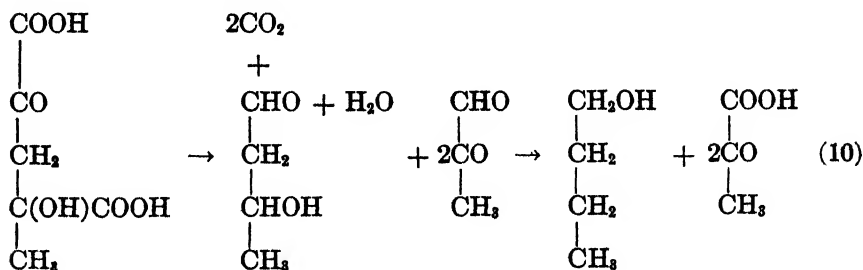
is broken in the middle to form two molecules of methylglyoxal.

In the process of fermentation without yeast cells, we find as intermedi-

ate products three esters of hexose with phosphoric acid, which carry the phosphoric groups at the end of the sugar molecule: 1) the ester of Harden-Young, fructofuranose-1,6-diphosphoric acid (16); 2) the ester of Neuberg, fructofuranose-6-phosphoric acid (18); 3) the ester of Robinson, glucopyranose-6-phosphoric acid (13, 28). As these hexosemono- and diphosphoric acids are fermentable as such with difficulty, it is probable that these intermediate products give rise to other products, in which the splitting of the carbon bond at the middle of the sugar molecule is facilitated. We shall suppose that these other products are the 1,2-dienols mentioned before. According to this thesis the rupture of the carbon chain of the glucose molecule is alike whether enzymes or alkalis are used. The process in both cases leads to the same intermediate products, the 1,2-dienols, in the first case by way of the above esters, in the second case, directly.

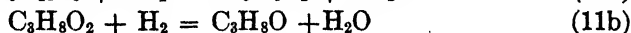
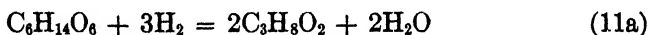
According to the double bond rule the location of the rupture must be different in the different dienols of hexoses: the 1,2-dienols will split off in the 3,4-position, the 2,3-dienols in the 4,5-position. In the first case compounds with three, in the second case compounds with four and two carbon atoms in the molecule are formed, and whether the numbers of carbon atoms in the chains are conserved or not depends on the conditions of reaction.

Amylum can be fermented by especial varieties of yeast with the formation of large amounts of butyl alcohol (38). Neuberg and Arinstein assume that this *n*-butyl alcohol is the product of a synthesis from smaller fragments which are formed in the process of fermentation (20). This assumption seems probable at first sight because Buchner and Meisenheimer (2) have found that glycerol, on fermentation with *Bac. butylicus*, gives butyl alcohol, ethyl alcohol, and carbon dioxide. Neuberg and Arinstein assume that the aldol of pyruvic acid, formed from pyruvic acid, is the intermediate product, and formulate the reaction as follows:

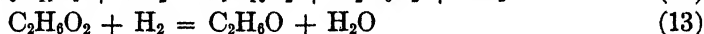


It is possible that the reaction proceeds thus in the above case, but it is not necessary that the scheme of reaction be the same in the case of amylum. It seems to be much more probable that chains with four carbon atoms are formed directly by the scission of a 2,3-dienol.

There is a process of rupture of carbon bonds in a chain of six carbon atoms which can be interpreted only on the latter basis, namely, the hydrogenating scission of hexitol. I have found (31) that this scission is effected by hydrogenating hexitols with catalysts of the second class (nickel, cobalt, etc.) under pressure (e.g., 300 atmospheres) at a temperature of about 200°C. This is the temperature at which *hydrogenating catalysts* of this class *have dehydrogenating properties*. The scission of sorbitol, mannitol, and dulcitol forms principally 1,2-propylene glycol and isopropyl alcohol, according to the equations:



These reaction products are also obtained if glycerol is hydrogenated under the same reaction conditions. Only a small part of the hexitol is split off to form chains of four and two carbon atoms—2,3-butylene glycol, ethylene glycol, and ethyl alcohol—according to the equations:



2,3-Butylene glycol is also obtained if erythritol is hydrogenated under the same conditions.

It is extremely improbable that in this high pressure hydrogenating process butylene glycol is formed from active fragments of scission, because such active fragments would first be hydrogenated and would then be unable to react together to form larger molecules. Therefore the same may be expected in the case of the sugar scission with enzymes and in alkaline solutions. That the hydroxyl groups at the ends of the molecule are reduced in the hydrogenating process is comprehensible because they are most accessible.

The pentoses react in a similar manner. Fischler and Boettner investigated the scission of arabinose with alkali (5) and obtained a mixture of methylglyoxal and glycolic aldehyde. According to the double bond rule we here also assume formation of a 1,2-dienol as intermediate product of the scission.

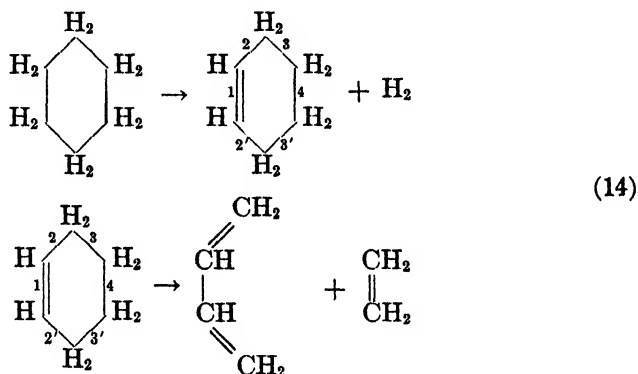
### B. The cracking process

The scission of the sugar molecule by enzymes and alkali is a process which takes place at ordinary temperature chiefly because the formation of a dienol with its weak bond is effected so easily by a simple isomerization at the room temperature. In the process of splitting hexitols by catalytic hydrogenation a much higher temperature of about 200°C. is needed; this is the temperature at which hydrogenating catalysts show dehydro-

genating properties. The first step of the reaction is the formation of a hexose.

The process of cracking paraffins proceeds according to a similar scheme. Here too the first reaction is the formation of a double bond by the splitting-off of two hydrogen atoms. The location of the double bond is then decisive for the location of rupture. This hypothesis is not the customary one. Heretofore it has been assumed that the breaking of a bond between two carbon atoms is the first step in the cracking reaction.

There is no doubt that by cracking cycloparaffins, such as cyclohexane, the greater part of the molecule is first dehydrogenated to tetrahydrobenzene and then split into two fragments, butadiene and ethylene, as I have shown (29). Therefore the series of reactions with primary dehydrogenation and scission on the weak positions 3 and 3' is experimentally well founded.



Only a small proportion of the molecules of cyclohexane is first split into hexylene, probably  $\alpha$ -hexylene, by first breaking a bond between two carbon atoms. In this case propylene, amylene, and its conversion products, 1-methylbutadiene and cyclopentadiene, are formed according to the following scheme:

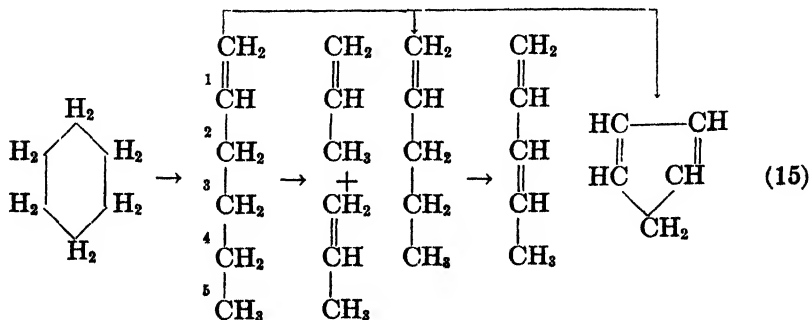




TABLE 2  
Results of cracking of normal paraffins

HYDROCARBON	TEMPERATURE	P	TIME OF HEATING	YIELD OF CRACKING PRODUCTS IN PER CENT	RESULT			AUTHOR
						Scission in	Amount in per cent	
<i>n</i> -Butane	°C.							
	600	1	1 min.	ca. 20	$\text{CH}_4 + \text{CH}_2=\text{CH}=\text{CH}_2$	1 2	44	Hurd (11)
	700	1		ca. 75	$\text{CH}_3\text{CH}_3 + \text{CH}_2=\text{CH}_2$	2 3	46	
					$\text{H}_2 + \text{C}_2\text{H}_4$ ; $2 \text{H}_2 + \text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$	5 4	5 4	
<i>n</i> -Pentane	600	1	19 sec.	ca. 17		1 2	55	Hurd and Spence (12)
	650	1	10 sec.	ca. 42		2 3	40	
						1 2	35	Hague and Wheeler (10)
						2 3	40	
<i>n</i> -Pentane	600	1	ca. 70 sec.	ca. 30	$\text{CH}_4 + \text{C}_2\text{H}_4$	1 2	20	Calingaert (4)
					$\text{CH}_2=\text{CH}_2 + \text{C}_2\text{H}_4$	2 3	25	
					$\text{C}_2\text{H}_6 + \text{CH}_3\text{CH}=\text{CH}_2$ , besides H	2 3	55	Norton and Andrews (22)
								Hague and Wheeler (10)
<i>n</i> -Hexane	600	1	1 sec.	ca. 73	$\text{CH}_4 + \text{C}_6\text{H}_{10}$	1 2		Haber (9)
					$\text{C}_2\text{H}_6 + \text{C}_4\text{H}_8$	2 3		Hurd (11)
					$\text{C}_2\text{H}_6 + \text{C}_3\text{H}_6$ , besides $\text{H}_2$ , $\text{C}_4\text{H}_6$ , $\text{C}_6\text{H}_{12}$	3 4		Norton and Andrews (22)
							Mean re-action	Hague and Wheeler (10)



improbable that the scission into *free* radicals is the main reaction if hydrocarbons of a higher molecular weight take part in the cracking process.

The time of impact, i.e., the length of time during which the two partners of the impact remain together, has the greatest influence on the course of the reaction. This time depends upon the velocity, the nearest distance  $d$ , which the impact partners reach, and this distance depends upon the "softness" of the partners of the impact (33). The "softness" is determined by the exponent  $n$  of the potential of repulsion,  $U_b$ , in

$$U_b = \frac{k_b}{r^n}$$

as calculated from the second virial coefficient (36). This exponent is small in the case of hydrocarbons which are soft. The longer the time of impact, the less probable is the formation of *free* radicals, which undergo change to form more stable compounds during the time of impact, i.e., of contact.

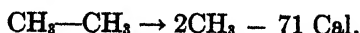
Senftleben and Hein (35) have investigated the processes of impact in the association of hydrogen atoms to molecules, and have found that this association is the more favored the higher the atomic weight of the inert gas in which the combination takes place.

It is remarkable that Rice observed only the methyl radical, which has the smallest mass. The higher radicals were not found, presumably because they were already transformed in the time of contact of the partners of collision.

Whichever of the various schemes given by Burk (3) and Rice (25) for the cracking process we adopt, the principle is always the same: the first step in the cracking reaction is the breaking of a C—C bond. Rice has justified this explanation by the following consideration (26). The work of dissociation of a C—C bond,  $Q_2$ , is smaller by 15 to 20 Cal. than the work of dissociation of a C—H bond,  $Q_1$ . If we consider a molecule capable of two types of dissociation having the activation energies  $E_1$  and  $E_2$ , respectively, then the relative rates of the two reactions are given by  $e^{\frac{E_1 - E_2}{2 \times T}} : 1$ , and we find that for a difference of 10 Cal. at 600° C. the reaction having the activation energy  $E_1$  can be completely neglected at the usual temperatures of the cracking process. Therefore according to Rice the splitting of a C—C bond is much more probable than that of a C—H bond and is the only one possible under the conditions of the cracking process; hereby it is assumed that the values of  $Q$  and  $E$  are proportional.

Let us consider the two reactions a little more precisely. In breaking a C—C bond two radicals are formed and an energy of about 71 Cal. is

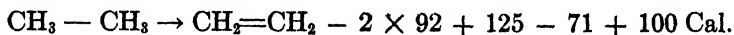
needed. These radicals are free, i.e., they have a relatively long life. Rice has found a value of about 0.006 second (27). Therefore we have:



In breaking two neighboring C—H bonds no hydrogen atoms but a hydrogen molecule is formed; the residual compound has a double bond between two carbon atoms. In this case the balance is quite different. We have



If we take the values for the different energies of dissociation given by Grimm (8) we find



and this reaction needs only 30 Cal. By using the known values of energy of formation we find that an energy of 43.7 Cal. is needed. Whatever the right value of the different dissociation energies may be, the whole energy needed in the reaction to break a C—H bond is much smaller than that needed to break a C—C bond, if free radicals are formed only in the last case. Therefore the course of the reaction depends upon the conditions of the experiment. Yet in the cracking of aliphatic hydrocarbons there can be no doubt that experiments show that the breaking of two C—H bonds and the formation of a double bond is the more frequent reaction.

We now repeat the result of our considerations. If two aliphatic hydrocarbons A come into collision and one of them is split, then in the time of contact the latter can first form two radicals with uncoupled valence electrons; and if there are mobile hydrogen atoms these radicals then undergo transformation during the time of contact.

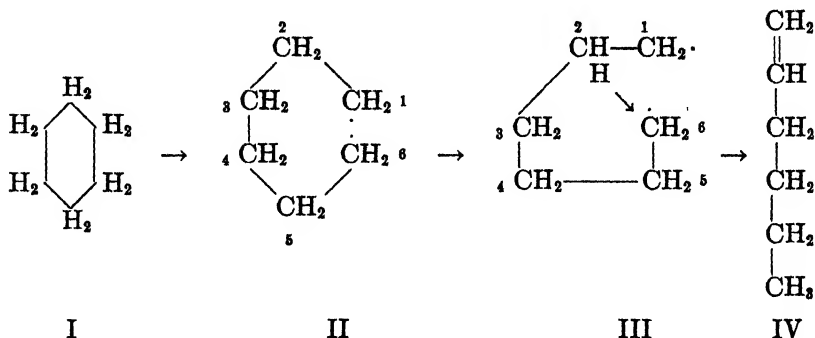
We may interpret the reaction between two molecules of simple hydrocarbons by the equation



where  $\text{A}^*$  is a molecule in a state of activation,  $\text{B}^*$  and  $\text{C}^*$  are radicals, and the expression on the right side indicates that the radicals formed are in contact with A. If the time of contact is short enough and the mobility of a radical is great, then it is possible that it escapes before transformation, as we have seen in the case of methyl with its low molecular weight. If there is no possibility of change, then of course radicals with large molecular weight are also stable under favorable conditions. Triphenylmethyl, which has no mobile hydrogen atoms and cannot change without incisive

transformations, is quite stable in oxygen-free solutions. Other radicals will undergo transformation to stable molecules in the time of impact (51).

We can now contemplate anew the process of cracking cyclohexane. As we have seen, in most of the molecules two C—H bonds are broken and tetrahydrobenzene is formed, which then gives butadiene and ethylene; but a small part of cyclohexane first gives  $\alpha$ -hexylene and a carbon bond is broken according to the scheme:



where the dots in formulas II and III indicate that there are free valences. Thus the hydrogen atom on the carbon atom 2 must travel to the carbon atom 6 to form the relatively stable product,  $\alpha$ -hexylene. The probability that such a shift takes place instead of the recombination to cyclohexane is the greater, the closer the hydrogen atoms of carbon atom 2 and carbon atom 6 come together, as is indicated in formula III. Finally  $\alpha$ -hexylene, with its double bond between atoms 1 and 2, is formed, and then undergoes further transformations in the cracking process as we have seen.

In a normal paraffin chain the binding forces between the carbon atoms of the chain can be assumed to be practically constant. Wierl (42) has measured the distances in Ångström units between the carbon atoms in a chain by his method of electron rays, as follows: ethane, C<sub>2</sub>H<sub>6</sub>, 1.52  $\pm$  0.1; propane, C<sub>3</sub>H<sub>8</sub>, 1.52  $\pm$  0.05; butane, C<sub>4</sub>H<sub>10</sub>, 1.52  $\pm$  0.05; pentane, C<sub>5</sub>H<sub>12</sub>, 1.53  $\pm$  0.05; hexane, C<sub>6</sub>H<sub>14</sub>, 1.54  $\pm$  0.05. Investigations with Röntgen-rays have shown that the dimensional increase of the elementary compound per CH<sub>2</sub> group in a series of homologous paraffins is completely constant, the value of this distance being 1.54 A. U. (6, 15, 37). The molecular volume also rises constantly in the series of normal paraffins; the same is true of the molecular refraction, which, according to Clausius-Mosotti, must be regarded as a measure of the volume occupied by the molecule.

We conclude from all these facts that the distances between the carbon atoms adjacent to one another in a paraffin chain are practically equal.

Since these distances are a measure of the binding forces between the carbon atoms, these forces are practically equal. At the ends of the chain we have a  $\text{CH}_3$  group instead of a  $\text{CH}_2$  group, but this difference probably has no appreciable influence because the distance between the carbon atoms in the molecule of ethane is the same as that in the molecule of propane, within the limit of experimental error.

If now the forces in a carbon chain of a normal paraffin are of the same strength, then the probability that the chain breaks up is the same for any C—C bond. For instance, in the molecule of *n*-pentane, with the bonds 1,2; 2,3; 3,4; and 4,5, the bonds 2,3 and 3,4 are equivalent and 1,2 and 4,5 are also. The probability that scission takes place at 1,2 is  $\frac{1}{4}$ , and that for 2,3 also  $\frac{1}{4}$ . In analogous manner we find the probabilities for the other hydrocarbons. But the results of the investigations do not conform to these calculations. Thus for pentane an 80 per cent scission at 2,3 was found, while the calculation gives 50 per cent. For chains of six carbon atoms the calculation gives a probability of 20 per cent at 3,4, whereas *n*-hexane gives more than 50 per cent; the scission of the sugar molecule and the hydrogenating scission of a normal hexitol take place with a yield of about 100 per cent at 3,4. Table 2 illustrates these relations.

Therefore the hypothesis that the first step in cracking consists of the scission of a C—C bond cannot be right. We conclude that the first step is in most cases the scission of two C—H bonds and that the double bond formed orients the place of scission according to the double bond rule.

If we suppose that the hydrogen atoms at the end of the chain are the most reactive because the end is most exposed to impacts, then the formation of a double bond is most probable at 1,2, and the C—C bond at 3,4 is weak according to the double bond rule; here the scission takes place. Indeed *n*-hexane is broken off chiefly at 3,4. Therefore the process of scission of sugar, the hydrogenation of hexitols under pressure, and the cracking process are governed by the double bond rule. Scission takes place in position 3, counting from the double bond as 1.

But according to the double bond rule, bond 5 is also weak, although less weak than 3. How is it possible that scission of sugar with yeast takes place only in position 3? Obviously this is a question of temperature. Let us suppose that the difference of the binding energy between the bonds 5 and 3 corresponds to an activation energy of about 6 Cal., which is probably nearly the right value. The proportion of velocities as between the two splitting reactions at 20°C. would be  $e^{\frac{6000}{2 \times 293}}:1 = 28,200:1$ . This means that the scission at 5 would be negligible because the velocity is 28,200 times smaller. If the difference were 5 Cal., the proportion would be 4,450:1. The proportion would decrease perceptibly only at higher temperatures.

Some observations indicate that scission at 5 takes place at higher temperature. We have seen that in the cracking of cyclohexane a part of the molecules form  $\alpha$ -hexylene, which gives principally propylene and in smaller amounts methylbutadiene and cyclopentadiene, two compounds with five carbon atoms. The proportion of chains or rings with three and five carbon atoms amounts to 30:1 at 710°C., and 11:1 at 755°C., if the cyclohexane remains in the contact chamber for ten seconds. The difference  $\Delta$  of the activation energy value in positions 5 and 3, is therefore found to be 6.7 Cal. and 4.9 Cal., respectively, with an average of 5.8.

A quite analogous case is that of cracking *n*-hexane, a reaction which Haber (9), Hurd and Spence (12), Norton and Andrews (22), Hague and Wheeler (10) have investigated. They found propylene as the main reaction product besides small quantities of amylene. Obviously at first  $\alpha$ -hexylene is formed by dehydrogenation, which then is split principally at position 3, in small amounts at position 5.

But some phenomena observed in the scission of sugar also indicate that scission at position 5 takes place in small amounts, as the theory requires. The presence of *n*-amyl alcohol in fusel oil, which Neuberg and Nord (11) established, finds its simplest explanation in the supposition that bond 5 is split off. The observation of Weinland, that in the action of the ferment of *ascaride* worms on the carbohydrates *n*-valeric acid is formed, is also interpreted most easily in the same manner.

If rupture of a 1,2-dienol or of a monoölefin has taken place at position 5 instead of at 3, the nascent product is unstable so long as it bears the double bond at 1. It still has a weak position at 3; only if a stable configuration is formed by an atomic displacement is the existence of the chain with five carbon atoms secured. In the process of cracking hexamethylene, methylbutadiene and cyclopentadiene are the stable products with five carbon atoms.

It would therefore be possible that the quantity of substances composed of five carbon atom chains, which is formed immediately after the scission, is larger than the quantity which is experimentally weighed, and that therefore the calculated difference of about 6 Cal. for the difference of the activation energy of the process of dissociation of the bonds 5 and 3 is too high. But clearly 5 Cal. is approximately the minimal value. A diminution to 3 Cal. would give a proportion of the velocities of scission of 167:1, and it is very improbable that an amount of scission at bond 5 of 1/167 would escape notice in such a carefully investigated process as fermentation.

The evidence of scission of the carbon bonds at 3 and 5 relative to the carbon double bond at 1 is of essential importance for the theory of the mechanism of splitting carbon bonds. Measured from center to center

of a bond, the distance between the bond 3 and the double bond is about 2.5 A. U., the distance of the bond 5 is about 5 A. U. This distance is so large that normal atomic forces of simple bonds do not play a part, because their influence does not go much over 2 A. U. (34). It will be the theme of later experimental investigations to solve these important questions.

## REFERENCES

- (1) BAKKER, A.: *Klin. Wochschr.* **1927**, 252.
- (2) BUCHNER, E., AND MEISENHEIMER, F.: *Ber.* **41**, 1410 (1908).
- (3) BURK, E.: *J. Phys. Chem.* **35**, 2448 (1931).
- (4) CALINGAERT, G.: *J. Am. Chem. Soc.* **45**, 130 (1923).
- (5) FISCHLER, F., AND BOETTNER, R.: *Z. physiol. Chem.* **177**, 264 (1928).
- (6) FREUDENBERG: *Stereochemie*, p. 113. Deuticke, Leipzig-Wien (1932).
- (7) FUERTH, O.: *Lehrbuch der physiologischen Chemie*, Vol. II, p. 295.
- (8) GRIMM, H. G.: *Handbuch der Physik*, Vol. 24, p. 536. Springer, Berlin (1927).
- (9) HABER, F.: *Ber.* **29**, 2691 (1896).
- (10) HAGUE, E. N., AND WHEELER, R. V.: *J. Chem. Soc.* **131**, 378 (1929).
- (11) HURD, C. D.: *The Pyrolysis of Carbon Compounds. The Chemical Catalog Co., Inc., New York* (1929).
- (12) HURD, C. D., AND SPENCE, L. U.: *J. Am. Chem. Soc.* **51**, 3354 (1929).
- (13) LEVENE, P. A., AND RAYMOND, A. L.: *J. Biol. Chem.* **92**, 757 (1931).
- (14) MARK, H., AND WIERL, R.: *Z. Physik* **60**, 741 (1930); *Physik. Z.* **31**, 366 (1930).
- (15) MEYER, K. H., AND MARK, H.: *Aufbau der Hochpolymeren*, p. 713 (1930).
- (16) MORGAN, W. TH. F., AND ROBINSON, R.: *Biochem. J.* **21**, 675 (1927); **22**, 1270 (1928).
- (17) NEF, J. U.: *Ann.* **357**, 300 (1907); **376**, 1 (1910); **403**, 204 (1914).
- (18) NEUBERG, C.: *Biochem. Z.* **191**, 450 (1927).
- (19) NEUBERG, C.: *Naturwissenschaften* **1930**, 427; *Biochem. Z.* **166**, 442 (1925).
- (20) NEUBERG, C., AND ARINSTEIN, B.: *Biochem. Z.* **117**, 269, 281 (1921).
- (21) NEUBERG, C., AND NORD, F. F.: *Biochem. Z.* **62**, 485 (1914).
- (22) NORTON, L. M., AND ANDREWS, C. W.: *Am. Chem. J.* **8**, 6 (1886).
- (23) See OPPENHEIMER, C.: *Fermente*, Vol. 2, p. 1450 (1930).
- (24) PEASE, R. N., AND DURGAN, E. S.: *J. Am. Chem. Soc.* **52**, 1264 (1930).
- (25) RICE, F. O.: *J. Am. Chem. Soc.* **53**, 1959 (1931).
- (26) RICE, F. O.: *Trans. Faraday Soc.* **30**, 152 (1934).
- (27) RICE, F. O., JOHNSTON, W. R., AND EVERING, B. L.: *J. Am. Chem. Soc.* **54**, 3529 (1932).
- (28) ROBINSON, R.: *Biochem. J.* **16**, 809 (1922).
- (29) SCHMIDT, O.: *Z. physik. Chem.* **159A**, 337 (1932).
- (30) SCHMIDT, O.: *Z. physik. Chem.* **159A**, 339 (1932).
- (31) SCHMIDT, O.: *Z. physik. Chem.* **159A**, 345 (1932).
- (32) SCHMIDT, O.: *Chem. Rev.* **12**, 363 (1933); see also *Ber.* **68**, 1098 (1935).
- (33) SCHMIDT, O.: *Ann. Physik* [5] **21**, 268 (1934).
- (34) SCHMIDT, O.: *Ber.* **67**, 1870 (1934).
- (35) SENFTLEBEN, H., AND HEIN, W.: *Physiker Tagung in Bad Pyrmont. Z. techn. Physik* **15**, 561 (1934).
- (36) STUART, H. A.: *Molekülbau*, p. 29. Springer, Berlin (1934).
- (37) STUART, H. A.: *Molekülstruktur*, p. 67. Springer, Berlin (1934).

- (38) ULLMANN, F.: *Enzyklopädie der technischen Chemie* **2**, 710 (1929).
- (39) WARBURG, O.: *Katalytische Wirkungen der lebenden Substanz*. Springer, Berlin (1928).
- (40) WARBURG, O., WITH MINAMI, S., POSENER, K., AND NEGELEIN, E.: *Biochem. Z.* **142**, 317ff. (1923); **152**, 309 (1924); *Klin. Wochschr.* 3/4 (1924, 1925).
- (41) WEINLAND, E.: *Z. Biol.* **43**, 86 (1902).
- (42) WIERL, R.: *Ann. Physik* [5] **13**, 453 (1932).
- (43) Free Radicals, *Trans. Faraday Soc.* **30**, No. 1 (1934).
- (44) CALINGAERT, G.: *J. Am. Chem. Soc.* **45**, 134 (1923).  
HURD, C. D.: *The Pyrolysis of Carbon Compounds*. The Chemical Catalog Co., Inc., New York (1929).
- (45) WILLIAMS, G.: *Trans. Roy. Soc. London* **1860**, 241.
- (46) KRAFFT, F.: *Ber.* **10**, 2034 (1877). See also BECKER, F.: *Ber.* **11**, 1412 (1878), and THOMS, H., AND FENDLER, G.: *Chem. Zentr.* **1901**, I, 612.
- (47) SCHMIDT, O.: *Z. physik. Chem.* **159A**, 345 (1932); German patent 252,499; U. S. patent 1,070,794.
- (48) STAUDINGER, H.: German patent 257,640.
- (49) BRUCHHAUSEN, F. VON, AND BERSCH, H. W.: *Arch. Pharm.* **266**, 697 (1928); *Chem. Zentr.* **1929**, II, 1700.
- (50) DIELS, O., AND ALDER, K.: *Ber.* **62**, 2343, 2359 (1929).
- (51) NORRISH, R. H. G.: *Trans. Faraday Soc.* **27**, 391 (1931). See also PATAT, F., AND SACHSSE, H.: *Naturwissenschaften* **23**, 247 (1935).

# THE NATURAL TANNINS

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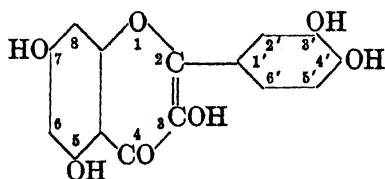
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## I. INTRODUCTION, PHYSIOLOGICAL SIGNIFICANCE, EXTRACTION, PROPERTIES

The name "tannin" covers a large range of naturally occurring compounds that are not necessarily structurally related and are widely distributed throughout the vegetable kingdom. The wood, bark, leaves, and roots of nearly all plants supply specimens, and they are particularly abundant in certain pathological growths such as oak galls, where the content may be as high as 80 per cent.

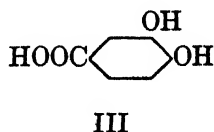
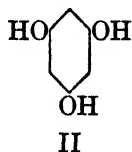
The physiological significance even of the normal members, as distinct from those occurring as a result of pathological processes, is not clear, although some relationships have been pointed out. A. G. Perkin (39) noted that the fission products given by tannins were, in some cases, the same as those given by the accompanying coloring matter; thus, quercetin (5,7,3',4'-tetrahydroxyflavonol (I))



I

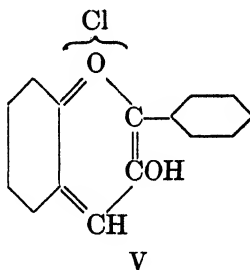
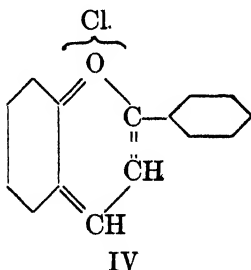


occurs in gambier and in acacia catechu associated with catechu tannin, and both quercitin and catechu tannin give, as fission products, phloroglucinol and protocatechuic acid (II and III).

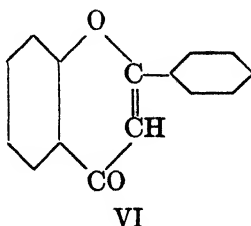


Other examples may be quoted: fisetin (7,3',4'-trihydroxyflavonol) occurs in quebracho Colorado and gives, by decomposition, resorcinol and protocatechuic acid; quebracho tannin gives the same pair of fission products. Sicilian sumach contains myricetin (5,7,3',4',5'-pentahydroxyflavonol) in the form of a glucoside,—myricitrin. On alkali fusion phloroglucinol and gallic acid result; the tannin also present gives the same decomposition products.

Similar results have been recorded by various botanists. Pick (52) found in some cases that as anthocyanin developed the tannin disappeared; anthocyanins are glucosides of anthocyanidins and these have the essential structures IV or V.



Much earlier Wiesner (63) noted, but did not make any appreciation of, the presence, side by side, of tannins and flavones: the essential flavone structure is shown in formula VI.



Other workers have noted like phenomena (36).

Attempts have been made to identify tannins as protective toxic materials inhibiting the growth of fungi (24), as fungi nutrients after enzymatic conversion by tannase to gallic acid (26), although this could only apply to gallotannin (which has been hydrolyzed by tannase), and, because of the seasonal variation in the quantity present, as reserve materials (25). The results described cannot, however, be accepted without qualification, as the tests often applied by botanists to identify tannins, such as the frequently occurring iron-greening property, are none too satisfactory; many plant products other than tannins give such a color with iron salts. It seems likely, nevertheless, that there may be some relationship between many tannins and the accompanying coloring matter of the benzopyran type. This expected relationship is the more interesting since it has now been established that many tannins are built on the benzopyran model.

Photosynthesis appears to play some part in the natural production of tannins, as they are more abundant in light than in etiolated shoots and, of the former, sun shoots have a higher content than shade shoots (30).

Tannins are amorphous, often hygroscopic, more or less soluble in water, and, in many cases, decompose somewhat in air and light, particularly if kept in a damp condition. When the difficulties of purifying crystalline plant products are appreciated, it will be realized how much greater these are where the usual criteria of purity are absent and where drastic methods of purification result in more or less extensive decomposition. All have the property in common of precipitating proteins from aqueous solution and this, although the exact nature of the change that occurs is not known, is generally supposed to form the basis of leather manufacture, the tannin converting the protein of the hide into a tough insoluble material that resists putrefaction. All tannins are polyhydroxylic phenols and, hence, have an astringent taste, are easily oxidized, and give colors or precipitates with various metallic salts.

Because of their technical importance and unusual nature the tannins attracted much attention until the past twenty years. However, more recently the subject has fallen somewhat into discredit, partly owing to the absence of constructive synthetic work but largely because of the prevalence of earlier theoretical speculations based on analytical results obtained from tannins of doubtful, obscure, or indefinite botanical origin. Other factors contributed to confusion, and a few of these need mentioning. Among them is the failure to recognize the existence of a large number of different tannins, to appreciate the difference between other members and gallotannin, the tannin present in oak galls, and the consequent careless application of the name "tannic acid" to any tanning material, to gallotannin itself, and, specifically, to digallic acid. The failure to specify tannins properly led to the publication of apparently contradictory results:

thus, oak tannin was confused with gallotannin till Eckert (6) realized the difference between them. More recently, it has been stated by Etti (7) that oak tannin is insoluble in water and gives a green color with ferric salts, whilst Löwe (27) and Böttinger (3) agree that the tannin is soluble in water and gives a blue color with ferric salts. These anomalous results are explained by the fact that oak wood tannin and oak bark tannin are different and give, respectively, blue and green colors with ferric salts. The insoluble oak tannin of Etti was probably the insoluble material—phlobaphene—produced by heating the tannin with acid. Again, commercial tanning extracts have often been used as sources of tannins, and technical extraction often involves the use of alkaline sulfites, bisulfites, sulfides, or even hydroxides. Whilst these reagents may not have affected seriously empirical tanning properties, their use may have caused extensive structural alterations and so rendered such extracts useless as sources of pure tannins.

For laboratory examination the tannin should be freshly extracted from its native source by the use of inert solvents; several have been employed for this purpose. Pelouze (37) used a mixture of alcohol, ether, and water, and even yet this is an important technical method of extracting gallotannin. The use of acetone was introduced by Trimble (60). This solvent has the advantage of not removing free sugar along with tannin; however, it extracts considerable amounts of insoluble coloring matters, resins, and waxes, and these must be separated afterwards. The following procedure is quite adequate for laboratory use where quantitative extraction of the bark or other material is not necessary. The dried and crushed material is extracted with cold water on the counter current principle and the extract treated with sufficient salt, whereupon the tannin precipitates as an amorphous solid. It is collected, dried in a vacuum, and the tannin separated by extraction, in a Soxhlet apparatus, with acetone. The acetone is removed on the water bath till the extract becomes very viscous; it is now transferred to a vacuum, when the tannin rapidly puffs up and dries. By washing the dried and ground material so obtained with ether a moderately homogeneous product results. For quantitative measurements the tannin must be dried in a vacuum pistol, using a suitable drying agent, at 100–120°C. for twenty-four hours or more, as traces of solvents are retained with great obstinacy. Too much emphasis cannot be laid on the necessity for adequate drying; the high analytical values recorded for hydrogen, and reports as to the presence of traces (0.5 to 5 per cent) of methoxyl in various tannins can only be attributed to the examination of insufficiently dried specimens that still contained some quantity of the solvent employed in extraction. Thus, Manning and Nierenstein (28) separated natural hemlock tannin in a somewhat arbitrary

fashion into seven fractions, and found that these had methoxyl contents varying from 0.80 to 3.56 per cent. In the procedure described resins, waxes, and insoluble materials are not removed from the bark, or other material extracted, by water; precipitation with common salt separates readily soluble impurities such as free sugar; extraction with acetone frees the tannin from inorganic materials; and washing with ether, in which tannins are insoluble, removes simple organic impurities. Tannins isolated in the manner described are light in color (fawn-pink), are readily and completely soluble in water, alcohols, ethyl acetate, and acetone, and insoluble in ether, hydrocarbons, or chloroform. Further purification through salt formation or other means is usually unnecessary and may even be harmful. It must be noted, however, that, since this and other methods of isolation and purification are largely empirical, individual tannins probably contain relatively large amounts of foreign material and a broad view must be taken of analytical results.

## II. CLASSIFICATION OF THE NATURAL TANNINS

The most satisfactory classification of tannins is that advocated by Perkin and Everest (41) by which the tannins are divided into three groups.

- I. Tannins related to depsides.
- II. Tannins related to diphenyldimethylid.
- III. Phlobaphene-producing tannins: phlobatannins.

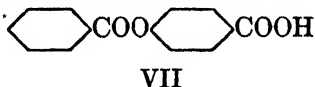
The group to which a particular member belongs is determined by boiling the tannin with dilute mineral acids, when the members of groups I and II hydrolyze giving crystalline fission products, gallic acid and glucose, and ellagic acid and glucose, respectively, whilst those of group III are completely converted into dark (red or brown) colored amorphous, insoluble phlobaphenes. Freudenberg (15) prefers to include the members of the first two groups in a single class as "hydrolyzable tannins." However, the Perkin and Everest classification is to be preferred, as the tannins related to depsides are quite different structurally from those related to diphenyldimethylid, in spite of the fact that both hydrolyze with dilute acids. Older classifications based on the colors produced by the tannins with ferric salts are meaningless, as such colors depend on the orientation of the free phenolic hydroxyl groups present and have no other structural significance. It seems that the members of group I are more particularly abundant in pathological growths; those of group II occur chiefly in certain nuts and pods; whilst group III includes the tannins present in wood, bark, leaves, and roots. So that the members of groups II and III are of physiological origin. Nevertheless, a classification into pathological and physiological tannins, which has been suggested, would be misleading as

the chief, and probably only, member of the first group is widely distributed in small quantities and may not always be of pathological origin. In view of the fact that most tannins belong to the phlobatannin class and the existence of only one member each of groups I and II has been established with certainty, it may eventually be unnecessary to consider classification at all and sufficient to regard tannins that do not produce phlobaphenes as exceptional members that happen to have the tanning property.

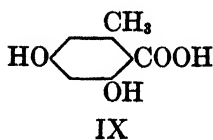
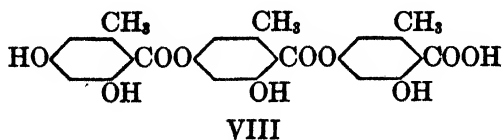
Various qualitative reactions in aqueous solution differentiate between phlobatannins and the others, the more important being the effects on phlobatannins of (1) dilute mineral acids to give phlobaphenes, (2) bromine water, giving an immediate heavy yellow-orange precipitate, (3) formaldehyde and dilute hydrochloric acid, to give immediate precipitation of a condensation product on warming, (4) potassium dichromate, giving an immediate brown or red-brown precipitate, (5) nitrous acid, giving an immediate brown or red-brown precipitate, and (6) lead acetate to give a light colored precipitate readily soluble in acetic acid. In order to identify definitely a given product as a tannin it is necessary to carry out a tanning test or some modified form of tanning test such as the goldbeaters' skin test recommended by Nierenstein (32).

### III. TANNINS RELATED TO DEPSIDES

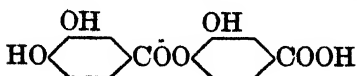
The depsides are crystalline substances occurring in small quantities in different varieties of lichens (53). They are acidic in character and derived from *p*-benzoyloxybenzoic acid (VII).



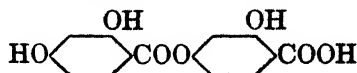
Ortho or meta coupling is exceptional. Didepsides contain two, tridepsides three, and tetradepsides four benzene nuclei, respectively. Most natural members are didepsides, and the different members have various hydroxyl patterns. Only one natural tridepside—gyrophoric acid—and no higher member is known, but synthetic polydepsides may be obtained without much difficulty (5, 9). Gyrophoric acid (VIII) is *p,p'*-triorsellinic acid (orsellinic acid (IX)) and its constitution has been established through the work of Hesse (21), E. Fischer (12), Y. Asahina (1, 2), and A. Robertson (4).



E. Fischer noted that certain depsides prepared by him, such as diprotocatechuic acid (X) and di- $\beta$ -resorcylic acid (XI), had tanning properties.



X

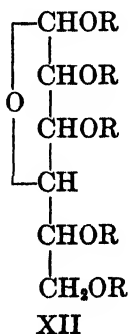


XI

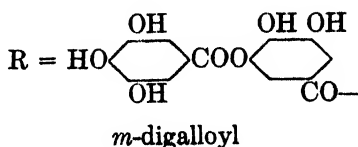
Only one natural tannin has been definitely linked to the depsides. Gallotannin (42) occurs chiefly in the galls produced by the puncture of insects on the leaves and buds of certain species of oak and sumach, but small amounts are often associated with other tannins. Aleppo and Chinese galls are the chief commercial sources of gallotannin.

By hydrolysis with dilute mineral acids glucose and gallic acid result and, by other methods of decomposition, pyrogallol; the pyrogallol presumably is formed by decarboxylation of gallic acid. Because of the accessibility of its crystalline fission products, gallotannin attracted much attention from the earlier chemists but, owing to the empirical methods of purification necessarily employed, much difficulty was experienced in determining the relative amounts of glucose and gallic acid resulting from hydrolysis. Indeed, gallotannin was reported to contain quantities of glucose varying from upwards of 20 per cent to none at all, the purer specimens containing less sugar. It seems certain, however, from the work of E. Fischer (9), Strecker (59), and others (42), that unaltered gallotannin is a glucoside and that, by acid hydrolysis, it gives nearly one molecule of glucose and ten molecules of gallic acid. E. Fischer therefore concluded that probably gallotannin was glucose fully esterified with five molecules of digallic acid, this being the most feasible way of accounting for the relative amounts of the fission products.

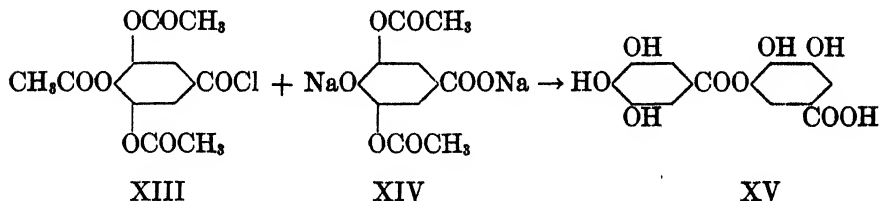
It having been shown that the digalloyl residues in gallotannin had the unusual (for depsides) meta coupling, in support of his view E. Fischer synthesized penta-*m*-digalloyl- $\alpha$ -glucose (10) and penta-*m*-digalloyl- $\beta$ -glucose (11).



XII



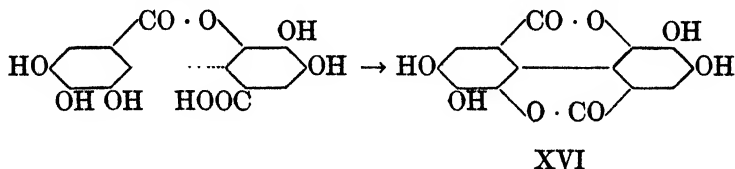
The synthesis of this unusual compound was carried out in the following way. Assuming that the digallic acid residues in gallotannin had the usual para coupling, triacetylgalloyl chloride (XIII) was condensed with disodium 3,5-diacetyl gallate (XIV). The resulting mixture of acetylated depside and acid anhydride having been separated with bicarbonate it was found, after deacetylation, that *m*-digallic acid (XV) had resulted.



The mechanism of this acyl migration is not clear, but from the point of view of the research its occurrence was advantageous rather than otherwise, since the depside obtained had the required meta configuration. Pentaacetyl-*m*-digalloyl chloride was condensed with glucose, by means of quinoline in solution in dry chloroform, to give the desired compound (XII) after deacetylation.

Penta-*m*-digalloylglucose compared very closely with natural gallotannin both qualitatively and quantitatively although, since both are amorphous, comparison of molecular weights was not satisfactory.

The value for combined sugar in specimens of natural gallotannin seldom reaches the figure required for penta-*m*-digalloylglucose, but, since the tannin is always associated with some free glucose, digallic acid, gallic acid, and ellagic acid (XVI), it is reasonable to accept E. Fischer's structure for unaltered gallotannin and to regard the other substances named as decomposition products. The occurrence of ellagic acid (XVI) need cause no confusion, since it may readily be obtained by treatment of gallotannin with alkali, resulting by oxidation of the *m*-digallic acid as shown below:—



It is to be expected then that small quantities of ellagic acid should accompany natural gallotannin. The earlier anomalous results with regard to the sugar content of the tannin are explained by the fact that gallotannin hydrolyzes readily, and repeated processes of purification cause more and more hydrolysis with the final production chiefly of digallic acid.

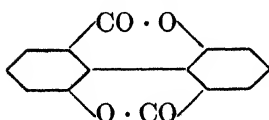
Taking the broad view then, it is probable that unaltered gallotannin is penta-*m*-digalloylglucose, but that commonly the natural tannin is a mixture of this compound with various decomposition products. It seems certain that it owes its tanning properties to the presence of the digalloyl residues in its structure and that the sugar plays no essential part since digallic acid, like the other depsides already mentioned, has tanning properties.

It must be pointed out, however, that Nierenstein (34) takes almost unqualified exception to Fischer's views and considers that gallotannin is a polydigalloyl-leucodigallic acid anhydride that may or may not be associated with glucose in the form of a glucoside.

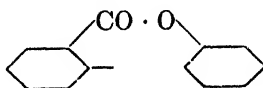
Various other hydrolyzable plant products have been recorded under the name "tannin." Some of these are crystalline. Some precipitate gelatin from aqueous solution; others do not. It should be noted that many non-tannins produce an insoluble precipitate with proteins, so that this property in itself is not sufficient to indicate the presence of a tannin. Two of these members appear to be structurally similar to gallotannin. Acer-tannin (49) occurs in the leaves of the Korean maple; it is crystalline and is accompanied by a much larger proportion of an amorphous variety. The crystalline product is stated to give, by acid hydrolysis, a molecule of aceritol and two molecules of gallic acid and is presumed to be digalloylaceritol. Hamameli tannin is also crystalline and gives an undetermined amount of gallic acid and an unidentified hexose as fission products (18). Since neither of these products appears to have been rigidly examined for tanning properties, their crystalline nature and apparently simple structure make it unlikely that they are really tannins. Their inclusion here is merely a matter of convenience and to avoid unnecessary multiplication of what may well be entirely speculative classes.

#### IV. TANNINS RELATED TO DIPHENYLDIMETHYLOLID

The parent substance of ellagic acid, the essential constituent of ellagitannin, is diphenyldimethylolid (XVII).



XVII



XVIII



XIX

Diphenyldimethylolid has not yet been prepared, but diphenylmethylole (XVIII) is well known and may readily be obtained by the method of Richter (52) through the action of phosphorus oxychloride on ethyl salicylate (XIX).



Ellagitannin, the only member of this group that has positively been identified, occurs chiefly in myrobalans, divi-divi, algarobilla, and valonia. Myrobalans are nuts of the *Terminalia Chebula* (China and the East Indies); divi-divi are the dried seed pods of *Caesalpinia coriaria* (West Indies, Central America); algarobilla are the pods of *Caesalpinia brevifolia* (Chile); valonia are acorn cups of certain oaks (Southern Europe).

The constitution of ellagitannin is not definite; it gives ellagic acid and glucose by acid hydrolysis and is therefore probably a glucoside of ellagic acid. However, Nierenstein (31) considers that some specimens of ellagitannin are mono- or poly-galloyl derivatives of ellagic acid and contain no sugar.

Ellagitannin or extracts containing ellagic acid are valuable constituents of tanning liquors, since ellagic acid produces the "bloom" on leather so desired by tanners. For this reason chestnut and oak extracts are highly prized, the phlobatannins chiefly present being accompanied by suitably large amounts of ellagic acid or of some component that produces ellagic acid readily. The chestnut extract referred to is that of the wood of the true chestnut, *Castanea vesca*: it is not to be confused with the horse chestnut, *Aesculus hippocastanum*, which yields a tannin of little practical value.

Ellagic acid and a number of its congeners have been prepared by the oxidation of simple phenolic acids with potassium persulfate (40), but the exact constitution of ellagitannin itself still awaits elucidation.

#### V. PHLOBAPHENE-PRODUCING TANNINS: PHLOBATANNINS

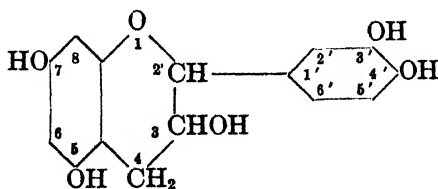
All those tannins, with the few doubtful exceptions already noted (acer-tannin, hamameli tannin), occurring as the result of normal physiological processes in the wood, bark, leaves, and roots of plants are phlobatannins. Because of their numerical preponderance and the ready accessibility of some or several members in all parts of the world, the phlobatannin group includes the most important tanning materials. Indeed, it is not at all certain, as has already been noted, that all classification of tannins is not somewhat artificial, phlobatannins representing the true tannin class, the others being exceptional members that happen to have tanning properties.

By treatment with boiling dilute mineral acids phlobatannins do not give recognizable hydrolytic products, but are slowly and completely converted into red or brown amorphous, insoluble materials that have been named *phlobaphenes* ("anhydride" or "tanners red"). In some cases, after acid treatment, traces of simple phenolic acids, protocatechuic or gallic acids, and of sugars are found. However, since many phlobatannins do not give them at all and the quantities are always very small, the occasional occurrence of phenolic acids in small amounts can be dismissed as due to some trivial decomposition, and of sugar to the presence of some

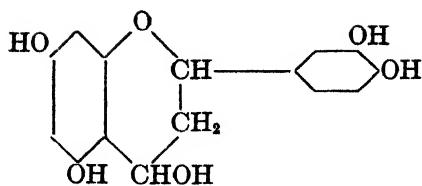
foreign glucoside. Owing to the empirical methods of purification necessarily adopted, the presence of traces of impurity is only to be expected. It must be noted too, that small amounts of gallotannin and ellagitannin are so frequently found associated with various phlobatannins that traces of gallic acid may often be detected even if the phlobatannin present contains no pyrogallol nucleus.

E. Fischer's convincing comparison of penta-*m*-digalloylglucose with natural gallotannin, and the fact that ellagitannin, although structurally different, is also probably a glucoside containing the  $\text{—CO.O—}$  group, have led to the erroneous supposition (43) that phlobatannins, too, are glucosides and related to depsides. This view is purely traditional and very misleading. It was not subscribed to at all by E. Fischer himself who, when abandoning the subject after his successful work on gallotannin, stated: "Aber die übrigen Bestandteil des natürlichen Tannin die nicht krystallisieren bleiben auch dann noch in ihrer chemischen Individualität unbekannt." There is no experimental evidence whatsoever for such a view; phlobatannins, as might have been supposed from their frequent occurrence side by side, are constituted in an entirely different manner and are related not to depsides or sugars, but to the normal plant pigments of the benzopyran type, flavones, flavonols, and anthocyanins. Their nearest analogues are the flavans, and therefore it is necessary to introduce here some account of catechin, as the solitary known natural member of the flavan group.

Catechin ( $\text{C}_{15}\text{H}_{14}\text{O}_6$ ) is a difficultly crystalline material that occurs in small quantities chiefly in certain varieties of "catechu" or "cutch." The botanical origin of commercial cutches is often obscure, but the best source of catechin is gambier catechu or terra japonica which is extracted from the leaves and twigs of *Uncaria gambier* (Malacca, Penang, Singapore). Catechin was first isolated by Nees van Esenbeck (61), and has been examined from time to time by various workers (46). By fusion with alkali it gives phloroglucinol, protocatechuic acid, and, probably, acetic acid; whilst catechin tetramethyl ether gives, by oxidation with permanganate, veratric acid and phloroglucinol dimethyl ether. A. G. Perkin (38) therefore considered that catechin was 3(or 4), 5, 7, 3', 4'-pentahydroxyflavan (XX or XXI),

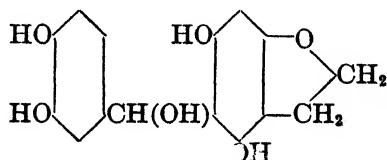


XX



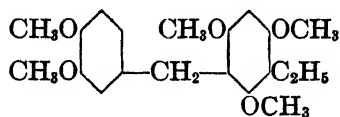
XXI

a reduction product of quercetin (see I), of which some quantity is present with catechin in gambier catechu. Von Kostanecki and Lampe (62) however, found that catechin gave only a monobromide readily and therefore abandoned Perkin's formula (which, it might be supposed, would brominate equally readily in positions 6 and 8) in favor of a constitution of the chroman type (XXII).



XXII

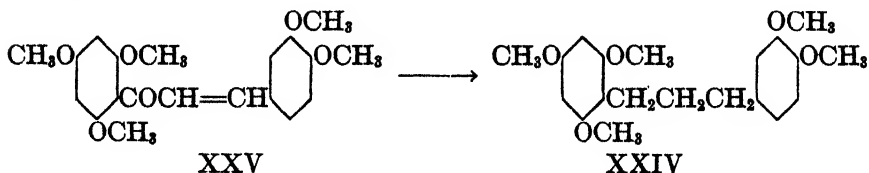
The same workers also claimed to have obtained pentamethoxyethyl diphenylmethane (XXIII) by reduction of catechin and methylation of the resulting oil.



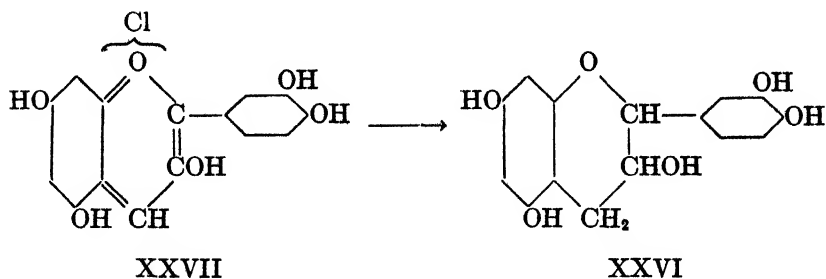
XXIII

However, Ryan and Walsh (58) could not identify the product obtained by von Kostanecki with synthetic pentamethoxyethyl diphenylmethane prepared by them in an unambiguous way.

Finally the constitution of catechin was established by K. Freudenberg in the following way. Reduction of catechin tetramethyl ether and methylation of the product gave a compound identical with that (XXIV) obtained by reducing 2,4,6,3',4'-pentamethoxychalcone (XXV) with hydrogen and platinum.

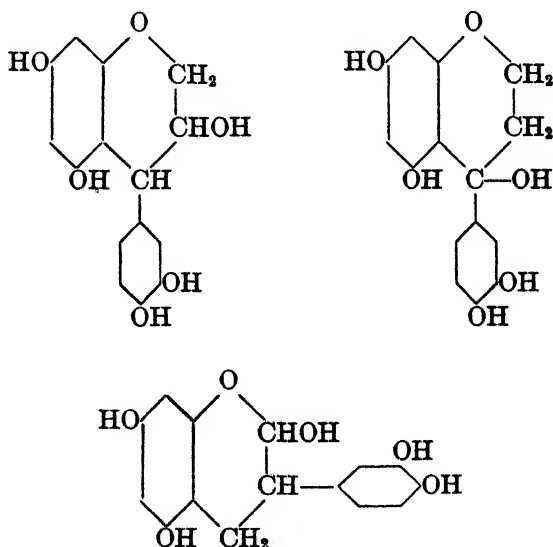


The production of a derivative of diphenylpropane points to the Perkin formula for catechin, and this was ultimately shown to be correct by Freudenberg's synthesis (19) of catechin (XXVI) from cyanidin chloride (XXVII) of known constitution.



Furthermore, similar reductions of both cyanidin chloride pentamethyl ether (see XXVII) and of quercitin pentamethyl ether (see I) gave catechin pentamethyl ether (see XXVI). It is, then, very fully established that catechin is 3,5,7,3',4'-pentahydroxyflavan.

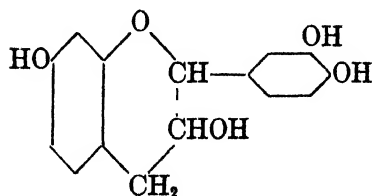
Freudenberg (16) has extended his work to a comprehensive stereochemical examination of catechin and has identified the six possible stereoisomers. Nierenstein (33) disagrees with Freudenberg's view and considers that some of the alleged stereoisomeric catechins are really structural isomers, the singly bound phenyl group occupying the 3- or 4-position instead of the 2-position. He submits three structurally isomeric formulas for catechin:



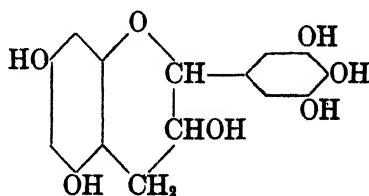
and claims to have recognized eight of the fifteen stereoisomers possible according to this scheme. However, the Perkin formula as advocated by Freudenberg is to be preferred, because of the more constructive nature of Freudenberg's work and because of its resemblance to the well authenticated formulas of the plant pigments.

Catechin-containing cutches and many others in which no catechin is present are used for tanning, since a phlobatannin, catechu tannin, is also present; more often they are associated with an oxidizing agent in an approximate tanning processes known as "barking," for waterproofing lines and cords. Barking processes are quite empirical, and it is not clear whether some change analogous to the tanning of hides occurs, or whether there is merely involved the deposition throughout the material of a relatively large amount of insoluble matter protecting the fibers from disintegration by water.

Catechin is not itself a tannin, but it resembles phlobatannins in some respects. It is crystalline, is converted, by boiling with dilute mineral acids, to an insoluble phlobaphene-like material, gives a colorless precipitate with lead acetate and a green color with ferric salts, but does not precipitate gelatin. Its fission products, phloroglucinol and protocatechuic acid, correspond to those given by catechu tannin and by many other phlobatannins (47). Freudenberg has therefore expressed the view that each phlobatannin is a polymer of that 3-hydroxypolyhydroxyflavan that gives fission products corresponding to those given by the tannin. If this attractive view is accepted and it is assumed that the relation between catechin and catechu tannin, which occur together, is a usual one, then it is to be expected that each phlobatannin should have accompanying it a corresponding 3-hydroxypolyhydroxyflavan. Unfortunately catechin is the only member of its class that has been identified as a natural product. Several synthetic congeners have been prepared by Freudenberg (17), namely, 3,7,3',4'-tetrahydroxyflavan and 3,5,7,3',4',5'-hexahydroxyflavan (XXVIII and XXIX).



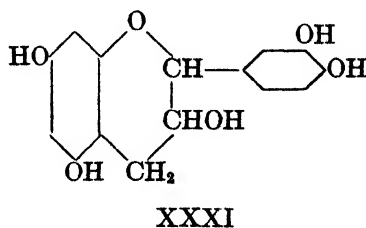
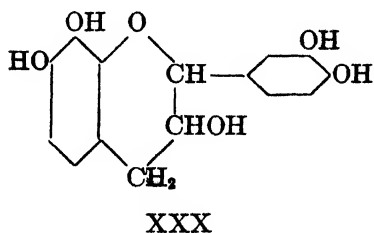
XXVIII



XXIX

From consideration of the various results recorded it seems certain that phlobatannins must be built on the catechin model; this has been established by A. Russell through the synthesis of a number of compounds of unambiguous structure that are qualitatively indistinguishable from typical natural phlobatannins. Where individual quantitative comparison has been possible there is also a close correspondence of values, but it is clear that the properties of the different members of the phlobatannin group are too alike to make comparison of synthetic products with individuals really convincing. Moreover, the difficulty of preparing amorphous compounds for exact quantitative comparison is too well appreciated to need emphasis.

A careful analytical examination of two typical members of the phlobatannin group, hemlock and mimosa tannins, newly extracted from hemlock and mimosa barks, respectively, was made and the fission products with fused alkali determined. It is somewhat desirable, but not necessarily essential, to examine freshly isolated tannins, since the exact behavior of a tannin depends to some extent on its previous history. Hemlock tannin, from the bark of the Canadian hemlock, gave as fission products pyrogallol, protocatechuic acid, and pyrocatechol (by decarboxylation of protocatechuic acid). Mimosa tannin, from South African mimosa or wattle bark, gave phloroglucinol, protocatechuic acid, and pyrocatechol. By acid treatment each was converted to a phlobaphene, and hemlock tannin gave a trace of glucose. \* Values of 60 to 62 per cent for carbon and of 4.5 to 4.9 per cent for hydrogen are, taken with the fission products, in agreement with the two corresponding pentahydroxyflavans (XXX and XXXI).



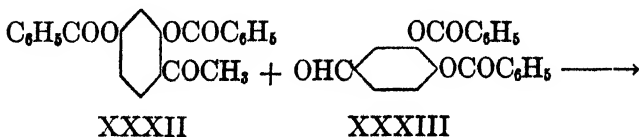
Purification of the tannins through their lead salts did not alter appreciably the values quoted except that, in the case of hemlock, the glucose was no longer detectable.

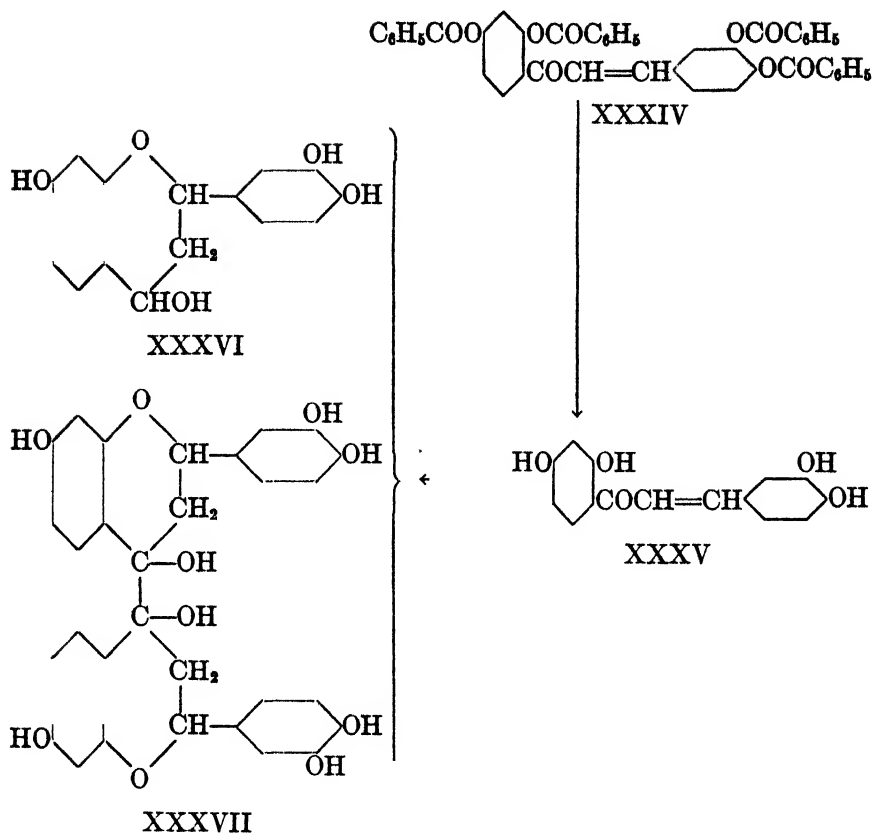
At this stage reference made to the results recorded (44) for numerous other phlobatannins showed that in every case are obtained, as fission products, a polyhydroxyphenol (phloroglucinol, resorcinol, or pyrogallol)

and a phenolic acid (protocatechuic or gallic acid). Amongst the decomposition products there may appear the phenol resulting by decarboxylation of the phenolic acid (pyrocatechol from protocatechuic acid, pyrogallol from gallic acid). Again, where the botanical origin is not definite, as in the case of quebracho tannin, or where wood and bark tannin of the same tree have not been separately identified, doubt may arise owing to the presence of two distinct phlobatannins. Allowance must also be made for the presence of traces of gallotannin and of ellagitannin in some cases. However, these various factors being considered, the recorded results may be interpreted in the manner stated.

The failure positively to identify phlobatannins as derivatives of 3-hydroxypolyhydroxyflavans led A. Russell (54) to suppose that in the phlobatannin structure the pyranoid hydroxyl might be in the 4-position instead of the 3-position, and experiments carried out to investigate this possibility led to the solution of the problem. Were this a normal synthetic problem dealing with crystalline compounds, trial experiments using methyl ethers and comparison of synthetic compounds with methylated natural products would be of value as a preliminary to the synthesis of similar polyhydroxy compounds. Since, however, comparison of natural with synthetic substances must be qualitative, tannins only being recognizable by their qualitative properties which depend largely, or even entirely, on the presence of free phenolic hydroxyl groups, and methylated natural tannins being amorphous and very poorly characterized, no comparison with synthetic methyl ethers could be of value. Therefore the synthesis of polyhydroxy compounds having the required flavan structure with the pyranoid hydroxyl in the 4-position was proceeded with.

Resacetophenone dibenzoate (XXXII) condensed with protocatechualdehyde dibenzoate (XXXIII) by means of anhydrous hydrogen chloride in solution in dry ethyl acetate to give 2,4,3',4'-tetrabenzoyloxychalcone (XXXIV), which, by debenzoylation in an atmosphere of nitrogen, gave the corresponding 2,4,3',4'-tetrahydroxychalcone (XXV). This, by reduction with zinc dust and dilute alcoholic acid, gave a pink amorphous compound that, by its mode of formation, must be either 4,7,3',4'-tetrahydroxyflavan (XXXVI) or the corresponding bis compound (XXXVII), —bis(7,3',4'-trihydroxy)flavpinacol.





The choice of phenol pattern was made partly for the sake of simplicity, difficulties of manipulation increasing greatly with increased numbers of phenol groups, and partly because quebracho tannin is probably hydroxylated on this pattern. Moreover, the intermediate 2,4,3',4'-tetrahydroxychalcone is a known natural product (butein), and the synthetic compound had properties identical with those given for natural butein (48).

The amorphous reduction product of 2,4,3',4'-tetrahydroxychalcone was qualitatively indistinguishable from typical natural phlobatannins as is shown in the table of reactions (table 1), and it may therefore be inferred that, whatever its structural make-up may be, phlobatannins are constituted in the same way.

The 0.5 per cent aqueous solutions used for the tests were each light yellow in color. In the later work, when the term "qualitatively indistinguishable" is used, the product referred to repeats with complete fidelity this list of tests. Of course the colors produced with the various salt-



forming reagents are not always the same, since these depend on the phenolic hydroxyl pattern.

TABLE 1

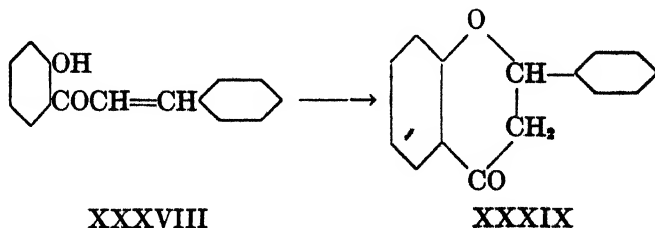
*Qualitative comparison of the reduction product of 2,4,3',4'-tetrahydroxychalcone with typical natural phlobatannins*

REAGENT	REDUCTION PRODUCT OF 2, 4, 3', 4'-TETRAHY- DROXYCHALCONE	HEMLOCK TANNIN	MIMOSA TANNIN
Alcoholic FeCl <sub>3</sub> .	Dark green color	Dark green color	Dark blue-violet color
Aqueous FeCl <sub>3</sub> .	Dark green color; dark blue precipitate	Dark green color; dark precipitate	Dark blue-violet color; dark precipitate
Gelatin . . . . .	Dirty white precipitate	Dirty white precipitate	Dirty white precipitate
Lead acetate ....	Light colored precipitate soluble in acetic acid	Light colored precipitate soluble in acetic acid	Light colored precipitate soluble in acetic acid
Boiling dilute HCl (phlobaphene reaction)... .	Solution reddens slowly and red precipitate separates	Solution reddens slowly and red precipitate separates	Solution reddens slowly and red precipitate separates
Bromine water .	Immediate heavy orange precipitate	Immediate heavy yellow precipitate	Immediate heavy orange precipitate
Calcium hydroxide..	Green color; faint green precipitate	Pink color; faint pink precipitate	Violet color; violet precipitate
Sodium sulfite... .	Pink color	Pink color	Pink color
HCHO + HCl ....	Precipitate on warming	Precipitate on warming	Precipitate on warming
Nitrous acid . .	Immediate brown precipitate	Immediate brown precipitate	Immediate brown precipitate
Copper sulfate ...	Faint green color	Faint green color	Faint green color
Copper sulfate + aqueous NH <sub>3</sub> . ...	Heavy dark precipitate	Heavy dark precipitate	Heavy dark precipitate
Aqueous ammonia..	Solution darkens slowly	Solution darkens slowly	Solution darkens slowly
Potassium dichromate . . . . .	Brown precipitate	Brown precipitate	Brown precipitate
K <sub>3</sub> Fe(CN) <sub>6</sub> + aqueous NH <sub>3</sub> . . . . .	Orange red color	Orange red color	Orange red color
Hide powder. ...	Absorbed quantitatively	Absorbed quantitatively	Absorbed quantitatively
Shaving of sheep-skin.....	Tanned	Tanned	Tanned

TABLE 1—*Concluded*

SOLVENT	REDUCTION PRODUCT OF 2, 4, 3', 4'-TETRAHY- DROXYCHALCONE	HEMLOCK TANNIN	MIMOSA TANNIN
	SOLUBILITIES		
Water . . . . .	Soluble: concen- trated solutions red, dilute solu- tions yellow	Soluble: concen- trated solutions red, dilute solu- tions yellow	Soluble: concen- trated solutions red, dilute solu- tions yellow
C <sub>2</sub> H <sub>5</sub> OH, CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> , (CH <sub>3</sub> ) <sub>2</sub> CO . . . . .	Readily soluble	Readily soluble	Readily soluble
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O, C <sub>6</sub> H <sub>6</sub> etc., ligroin, CHCl <sub>3</sub> , etc. . . . .	Insoluble	Insoluble	Insoluble
Sodium hydroxide	Readily soluble; dark solution bleached by acid	Readily soluble; dark solution bleached by acid	Readily soluble; dark solution bleached by acid

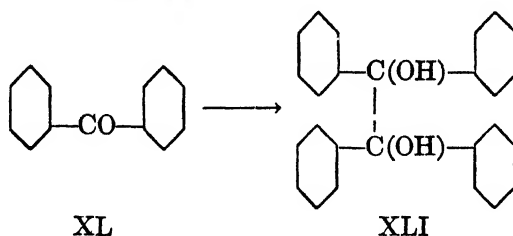
The exact constitution of the amorphous reduction product of 2,4,3',4'-tetrahydrochalcone was finally established in a somewhat roundabout fashion. A series of similar reduction experiments with a number of other 2-hydroxychalcones was carried out, and in every case an exactly similar amorphous product resulted; the reaction is therefore a general one for 2-hydroxychalcones. In those cases where the hydroxyl group in the 2-position in the chalcone was the only free one, the reaction products were totally insoluble even in warm normal alkali; hence, during the change, at least the pyran ring must have closed. Moreover, the experimental conditions favor and were designed to favor ring closure. If, under the mild conditions used, ring closure without reduction had occurred, the products would have been flavanones (XXVIII  $\rightarrow$  XXXIX), which are colorless, or nearly so, and readily crystalline.



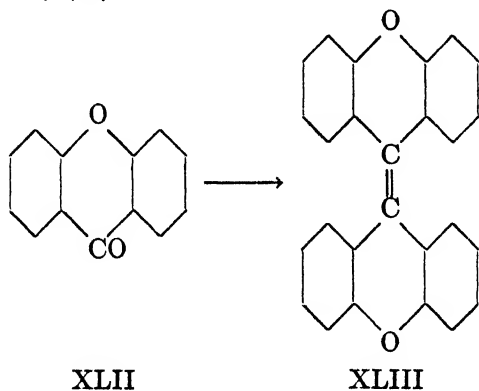
The products are not flavanones; therefore simultaneous ring closure and reduction must have occurred with the formation of flavans or flavpinacols. That is, the amorphous reduction product of 2,4,3',4'-tetrahydroxy

chalcone must be either XXXVI or XXXVII. Analytical values will not distinguish between these two, and molecular weight determinations are not practicable for amorphous compounds, but the flavpinacol structure was finally shown to be correct.

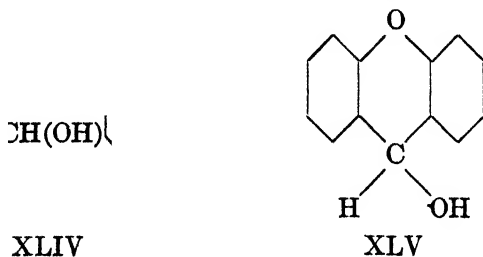
The flavan structure is unlikely, since the known 3-hydroxyflavans and all similarly constituted compounds of the benzopyran type are crystalline. Moreover, ketones commonly reduce to compounds of the bis type with zinc dust and acids; it is well known that benzophenone (XL) reduces to benzpinacol (XLI) in this way:



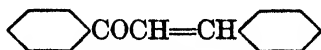
and, under more vigorous conditions, xanthone (XLII) gives dioxyxanthylene (XLIII) (20).



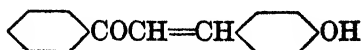
Whereas, by reduction with zinc dust and alkali, the same two ketones give, respectively, benzhydrol (XLIV) and xanthydrol (XLV) (29).



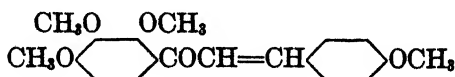
To find if the reaction went in a similar fashion using phenyl styryl ketones (chalcones), a series of chalcones was prepared of which the members had no free phenol group in the 2-position; the members selected were chalcone (XLVI), 4'-hydroxychalcone (XLVII), and 2,3,4,4'-tetramethoxychalcone (XLVIII).



XLVI



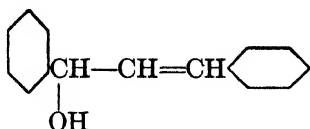
XLVII



XLVIII

By treatment with zinc dust and dilute alcoholic acids each of these gave a high-melting crystalline reduction product; that from chalcone itself, being readily obtained, was subjected to a somewhat extended examination.

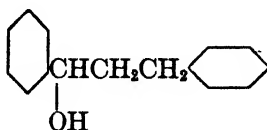
Chalcone ( $C_{15}H_{12}O_6$ , m.p.  $56-57^\circ C.$ ) forms light yellow needles. Its reduction product forms colorless needles, m.p.  $197^\circ C.$ , and has the empirical formula  $C_{15}H_{13}O$ . The simple (unimolecular) reduction products of chalcone are diphenylallyl alcohol (XLIX), m.p.  $56^\circ C.$  (35), hydrochalcone (L), m.p.  $72^\circ C.$  (22, 50), and hydrochalc醇 (LI), b.p.  $330^\circ C.$  (22, 50).



XLIX



L



LI

By comparison with these it was concluded that the product under examination was bimolecular, and this was confirmed by determinations of molecular weight. The similarly obtained reduction products of 4'-hydroxychalcone and 2,3,4,4'-tetramethoxychalcone must be bimolecular too. Since, like the other ketones mentioned, simple chalcones are thus shown to polymerize on reduction, it is in the highest degree probable that in the case of 2-hydroxychalcones the reaction follows the same course and that the reduction products of these are likewise of the bis type.

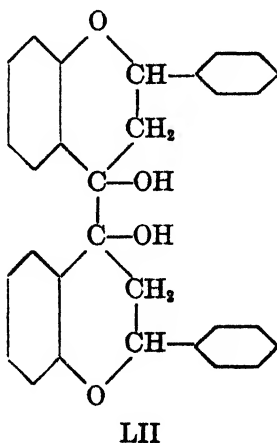
Finally, direct evidence of polymerization was obtained. Comparison of the two courses the reaction may have taken shows that for the production of the flavan one molecule of chalcone absorbs two equivalents of hydrogen (equation 1), whilst for the flavpinacol only one molecule of hydrogen for each molecule of chalcone is needed (equation 2).



Reduction of various 2-hydroxychalcones in a closed system, each experiment controlled by a blank, and measurement of the volume of hydrogen absorbed during reduction showed that the amount of hydrogen taken up corresponded to the amount required for the production of flavpinacols (55). The examples given in table 2 illustrate the order of correspondence obtained.

Therefore it may finally be concluded, retaining the standard nomenclature, that the reduction product of 2,4,3',4'-tetrahydroxychalcone is bis(7,3',4'-trihydroxy)flavpinacol, and, since this compound is qualitatively indistinguishable from typical natural members, that natural phlobatannins are built on the same model.

Phlobatannins are, then, phenolic hydroxy derivatives of flavpinacol (LII):



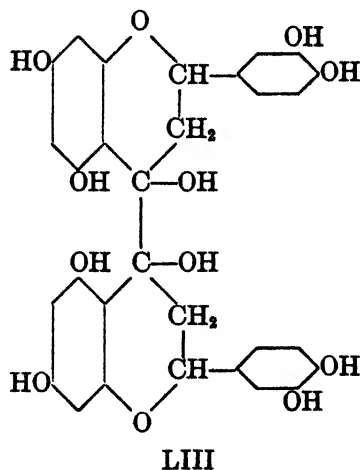
The phenolic hydroxyl pattern of individual members is indicated by the fission products given with alkali. Thus quebracho tannin gives resorcinol and protocatechuic acid, indicating that it is hydroxylated on the pattern of the flavpinacol just described—bis(7,3',4'-trihydroxy)flavpinacol. The alternative phenol pattern that would produce resorcinol

on decomposition, required for bis(5,3',4'-trihydroxy)flavpinacol, is improbable on general considerations of other plant products.

TABLE 2  
*Hydrogen absorbed by 2-hydroxychalcones during reduction*

CHALCONE	WEIGHT	HYDROGEN ABSORBED	HYDROGEN REQUIRED	
			Flavan	Flavpinacol
	grams	cc.	cc.	cc.
2-Hydroxy-3,4-dimethoxy.....	0.2009	7.3	16.0	8.0
2-Hydroxy-3,4,4'-trimethoxy . . . . .	0.2396	9.2	17.2	8.6
2,4,4'-Trihydroxy . . . . .	0.2074	7.8	18.1	9.1
2,4,3',4'-Tetrahydroxy . . . . .	0.1548	5.3	12.8	6.4
2,4,6,3',4'-Pentahydroxy . . . . .	0.3040	9.7	22.4	11.2

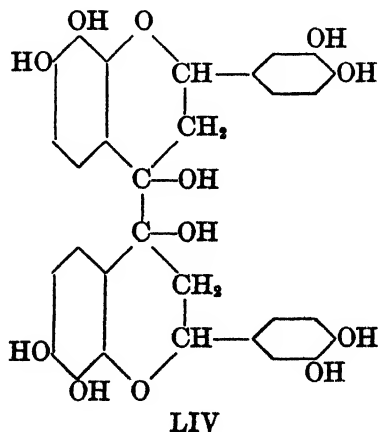
Some twenty phlobatannins give as fission products phloroglucinol and protocatechuic acid. These must be essentially hydroxylated on the pattern of bis(5,7,3',4'-tetrahydroxy)flavpinacol (LIII).



Assuming that the number of individuals is as great as this, individual differences are probably accounted for by partial alkylation of the phenol groups and the presence of various nuclear substituents, such as carboxyl, formyl, methyl etc., that would disappear during alkali fusion. This flavpinacol was obtained by the same general route as before described from phloroacetophenone tribenzoate and protocatechualdehyde dibenzoate, and it also is qualitatively indistinguishable from typical natural phlobatannins (55).

Hemlock tannin gives pyrogallol and protocatechuic acid as fission products. Extracts of hemlock are not so extensively used as they might be for tanning, since the leather produced has the deep red color of the solutions. The fission products indicate that the tannin is hydroxylated on the pattern of bis(7,8,3',4'-tetrahydroxy)flavpinacol (LIV). Since no other phlobatannin appears to give pyrogallol as its phenolic component, the natural tannin may even be identical with the flavpinacol, and quantitative comparison was therefore made between the two. The departure of hemlock tannin from the usual phloroglucinol or resorcinol pattern may well account for the unusually high color of its solutions; amongst natural products of the benzopyran type and in the case of polyhydroxychalcones, multiplication of phenolic groups ortho to each other produces a deepening of color. The absorption spectra measurements that will be described presently show that phlobatannins have no absorption in the visible, so that their colored solutions are due to the presence of traces of highly colored decomposition products; nevertheless, the explanation offered still holds good.

The synthesis of bis(7,8,3',4'-tetrahydroxy)flavpinacol (LIV) has been carried out by Russell and Todd (56) from gallacetophenone tribenzoate (2,3,4-tribenzoyloxyacetophenone) and protocatechualdehyde dibenzoate by the same route as before described; the synthetic product reproduces exactly the qualitative properties of natural hemlock tannin. Because of the unusual (for natural products) phenolic hydroxyl pattern indicated for hemlock tannin by its fission products, these were repeatedly examined for phloroglucinol and resorcinol, but neither could be detected. Should, in spite of this, another phenolic residue be found eventually amongst the decomposition products of hemlock tannin, the results just described would at least indicate that flavpinacols hydroxylated on the 7,8,3',4' pattern are phlobatannins.

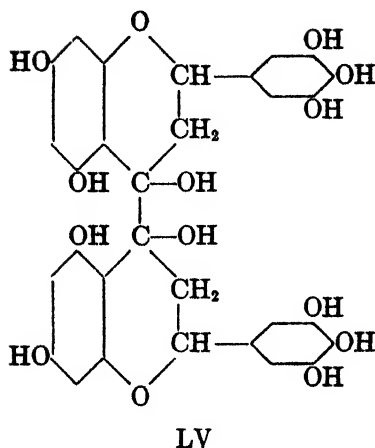


A quantitative comparison was also very close, as is illustrated by the values in the following list: Bis(7,8,3',4'-tetrahydroxy)flavpinacol: found C, 62.0; H, 4.55.  $C_{30}H_{26}O_{12}$  requires: C, 62.2, H, 4.5 per cent. Crude hemlock tannin: found, C, 61.7, 62.7; H, 4.9, 4.5 per cent. Purified hemlock tannin: found, C, 62.0; H, 4.4 per cent. Lead (hemlock) tannate: found, Pb, 27.3, 28.2.  $C_{30}H_{24}O_{12}Pb$  requires: Pb, 27.6 per cent. Methylated hemlock tannin (methyl sulfate and alkali): found, C, 66.5; H, 6.15;  $OCH_3$ , 31.8, 32.6.  $C_{30}H_{18}O_4(OCH_3)_8$  requires: C, 66.1; H, 6.1;  $OCH_3$ , 36.0 per cent.

Having obtained a sufficient number of synthetic polyhydroxyflavpinacols, the next step was a comparison of their absorption spectra with those of natural phlobatannins, and here the results obtained (57) verified the previous conclusions. The spectra of the parent polyhydroxychalcones of the polyhydroxyflavpinacols, and of the natural tannins are compared. The chalcone spectrum consists of a pair of moderately sharp bands in the ultra-violet with heads at about  $\lambda$  2690 and  $\lambda$  2890, together with a broad "color" band partly in the visible region with its head at about  $\lambda$  3900 (accounting for the complementary yellow-red color of the chalcones.) On reduction of the chalcone, corresponding to the destruction of the chromophoric character of the molecule, the "color" band disappears with little alteration in the rest of the spectrum. The flavpinacol spectrum consists of a pair of bands in the ultra-violet with heads at  $\lambda$  2700 and  $\lambda$  2870 corresponding exactly to the spectra of natural hemlock and mimosa tannins where the band heads measure at  $\lambda$  2700 and  $\lambda$  2860. The various flavpinacol spectra differ no more from each other than from the tannin spectra or than the tannin spectra do from each other. In the same paper (57) incidental measurements are included of the absorption spectra of gallotannin and of ellagic acid; these differ completely both from each other and from the phlobatannin spectrum.

A brief summary may be included of results further obtained by A. Russell and his collaborators. A number of phlobatannins (tea, pistachia, maletto, oak wood) give blue-black colors with ferric salts and, as fission products, phloroglucinol and gallic acid (or pyrogallol by decarboxylation). According to the views now under examination these must be hydroxylated essentially on the pattern of bis(5,7,3',4',5'-pentahydroxy)flavpinacol (LV). Prepared by the usual route this flavpinacol gives a blue-black color with ferric salts and has all the reactions of phlobatannins (compared with tea tannin).





There have now been obtained flavpinacols hydroxylated essentially on all the patterns indicated by the fission products determined or recorded for natural phlobatannins and the research has been extended to a comprehensive synthetic examination of flavpinacols having various other phenol patterns, with a view to determining what orientations of phenolic hydroxyl groups are essential to phlobatannin properties. Some of these may eventually find representatives amongst natural phlobatannins.

It has been found that all flavpinacols hydroxylated in the 3', 4'-positions are phlobatannins, whatever the phenol pattern of the rest of the molecule. In addition to the three members already described the following three have the necessary properties (the parent hydroxy ketone and aldehyde are included for each member): bis(6, 3', 4'-trihydroxy)flavpinacol, quinacetophenone, and protocatechualdehyde; bis(5, 3', 4'-trihydroxy)flavpinacol, 2, 6-dihydroxyacetophenone, and protocatechualdehyde; bis(3', 4'-dihydroxy)flavpinacol, *o*-hydroxyacetophenone, and protocatechualdehyde.

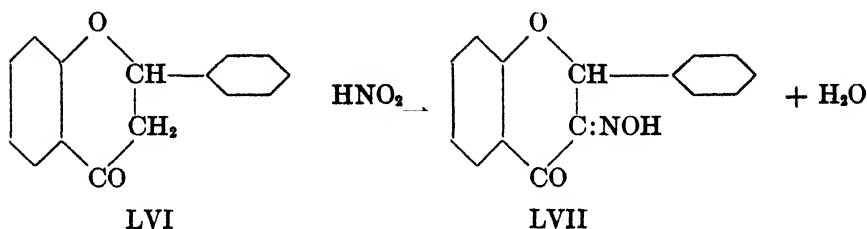
Qualitatively indistinguishable from phlobatannins are also: bis(5, 7, 2', -3', 4'-pentahydroxy)flavpinacol, phloracetophenone, and 2, 3, 4-trihydroxybenzaldehyde (pyrogallaldehyde); bis(5, 7, 2', 4', 6'-pentahydroxy)flavpinacol, phloracetophenone, and 2, 4, 6-trihydroxybenzaldehyde (phloroglucinaldehyde); bis(5, 7, 2', 4'-tetrahydroxy)flavpinacol, phloracetophenone, and 2, 4-dihydroxybenzaldehyde (resorcyaldehyde); bis(5, 7, 2', 4'-tetrahydroxy-6'-methyl)flavpinacol, phloracetophenone, and 2, 4-dihydroxy-6-methylbenzaldehyde (orcyaldehyde).

In spite of the encouraging nature of the results just described, until more detailed examination, in the light of present information, has been made of them, it would be idle to indulge in much speculation as to the meaning of the various reactions of the phlobatannins. Of course many

are due simply to salt formation and can be dismissed at once; of the remainder little need be said.

The formation of phlobaphenes may involve some change analogous to the pinacol-pinacoline rearrangement, and to this view is lent support by the observation that each phlobaphene appears to consist of two components of similar composition but differing greatly in solubility; one part (5 to 10 per cent of the whole) being readily soluble in alcohol and the other insoluble. Furthermore, conversion of tannin to phlobaphene seems to be accompanied by the loss of a single molecule of water.

The precipitate given with nitrous acid may be an isonitroso compound formed in an exactly analogous manner to the well-known isonitroso-flavanones (LVI  $\rightarrow$  LVII).

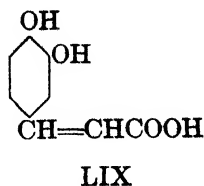
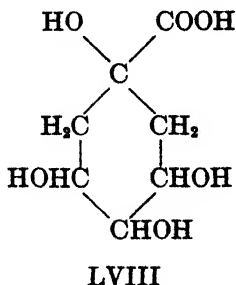


The bromotannins obtained by the action of bromine water contain upwards of 40 per cent of halogen and are likely to be just polybromophenols, their formation having little structural significance, although this offers no explanation as to why gallotannin, also essentially a polyhydroxyphenol, does not readily give a similar compound.

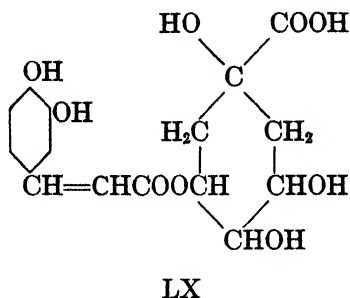
The very characteristic formaldehyde reaction appears to be due to the formation of a condensation compound.

#### VI. CAFFETANNINS

The various caffetannins extracted from different coffee berries and recorded in the literature (45) as tannins do not precipitate proteins and therefore certainly should not properly be identified with this group of natural products at all. By hydrolysis result quinic acid (LVIII), caffeic acid (LIX), and a residue of unknown composition.



The constitution of quinic acid has been established by H. O. L. Fischer and his collaborators (13). Caffetannins are usually associated in nature with chlorogenic acid, for which the constitution (LX) has been established synthetically also by H. O. L. Fischer (14).



It is likely then that caffetannins are closely related to or even identical with chlorogenic acid.

## VII. SUMMARY AND CONCLUSION

1. The methods of classification applied to that group of natural products of which the members have tanning properties are probably somewhat artificial since, with a few well-defined exceptions, all are phlobatannins. It is likely, too, that many natural products have tanning properties, although they have never been used as tannins and never recognized as such owing to the greater abundance and more ready accessibility of other materials. Thus, many, probably all, depsides that have more than an optimum number of free phenol groups, and, probably, many polyhydroxy-chalcones and polyhydroxyphenols of the benzopyran type have tanning properties.

2. Gallotannin occurs chiefly in oak galls, as a result of pathological processes, but small amounts are frequently associated with phlobatannins. It is likely, from the work of E. Fischer and his collaborators, that unaltered gallotannin is penta-*m*-digalloylglucose, but commonly the tannin is a mixture of this compound with various decomposition products. That it owes its tanning properties to the presence of the digalloyl residues present in its structure, the sugar playing no essential part, appears certain, since many depsides, including digallic acid itself, have tanning properties. Gallotannin is the only member of its class that has been properly authenticated, although acer-tannin and hamameli tannin may have somewhat analogous structures.

3. The constitution of ellagitannin is obscure but, from its fission products, glucose and ellagic acid, it is probably a glucoside of ellagic acid. Ellagic acid is a valuable constituent of tanning liquors, producing the much desired "bloom" on leather. The value of certain extracts, such as chestnut and oak, is much enhanced by the fact that the phlobatannins chiefly present are accompanied by suitably large amounts of free or combined ellagic acid.

4. Most of the natural tannins, and apparently all those occurring as normal products of physiological life in the wood, bark, and leaves of almost all plants, are phlobatannins. They are not related to depsides, as are gallotannin and ellagitannin, but are polyhydroxyflavpinacols derived from the corresponding 4-hydroxyflavans and are related to the usual plant pigments of the benzopyran type. Flavpinacols hydroxylated on the essential phenol patterns of the natural phlobatannins have been prepared by A. Russell and his collaborators by reduction of 2-hydroxypolyhydroxy-chalcones having suitably oriented phenolic hydroxyl groups. Qualitatively, quantitatively (where comparison has been practicable), and by exact absorption spectra measurements, the synthetic polyhydroxyflavpinacols are indistinguishable from typical natural phlobatannins.

5. The various caffetannins recorded in the literature do not possess tanning properties. They appear to be closely related to chlorogenic acid, although it cannot be said whether one or several members exist.

#### VIII. GRAPHIC SUMMARY OF THE RELATIONS BETWEEN THE VARIOUS PLANT COLORING MATTERS OF THE BENZOPYRAN TYPE

In view of the connection now established between phlobatannins and the common plant pigments, it would seem of interest to summarize graphically the interrelations between the members. The changes shown have all been carried out *in vitro* and it is probable that such, or similar, transformations *in vivo* form part of the regular plant economy.



## IX. REFERENCES

- (1) ASAHINA, Y., AND FUJIKAWA, F.: Ber. **65B**, 983 (1932).
- (2) ASAHINA, Y., AND WATANABE, M.: Ber. **63B**, 3044 (1930).
- (3) BÖTTINGER: Ber. **20**, 761 (1887) and earlier papers.
- (4) CANTER, F. W., ROBERTSON, A., AND WATERS, R. B.: J. Chem. Soc. **1933**, 493.
- (5) CURRIE, T., AND RUSSELL, A.: J. Chem. Soc. **1932**, 202.
- (6) ECKERT: Vierteljahrschr. prakt. Pharm. **13**, 494 (1864).
- (7) ETTI: Monatsh. **1**, 262 (1880); **3**, 512 (1882); **4**, 518 (1883); **10**, 805, 647 (1889); Ber. **14**, 1826 (1881); **17**, 1820 (1884).
- (8) FERNBACH: Compt. rend. **131**, 1214 (1900).
- (9) FISCHER, E.: Collected papers, "Untersuchungen über Depside und Gerbstoffe."
- (10) FISCHER, E., AND BERGMANN: Ber. **51**, 1769 (1918).
- (11) Reference 10, p. 1775.
- (12) FISCHER, E., AND FISCHER, H.: Ber. **46**, 1142 (1913).
- (13) FISCHER, H. O. L., AND DANGSCHAT, G.: Ber. **65B**, 1009 (1932) and earlier papers.
- (14) Reference 13, p. 1037.
- (15) FREUDENBERG: Ber. **53**, 1416 (1920).
- (16) FREUDENBERG: Tannin, Cellulose, Lignin, 2nd edition. J. Springer, Berlin (1933).
- (17) Reference 16, p. 53.
- (18) FREUDENBERG AND COLLABORATORS: Ber. **52**, 177 (1919); **53**, 953 (1920); Ann. Chem. Pharm. **440**, 45 (1924).
- (19) FREUDENBERG, FIKENTSCHER, HARDER, AND SCHMIDT: Ann. **444**, 135 (1925).
- (20) GURGEGANZ AND VON KOSTANECKI: Ber. **28**, 2310 (1895).
- (21) HESSE: J. prakt. Chem. [2] **62**, 321 (1900); [2] **92**, 466 (1915).
- (22) HÜBNER AND HERRIES: Ann. **296**, 326 (1897).
- (23) KATIC: Botan. Centr. **99**, 563 (1905).
- (24) KESELING: Botan. Centr. **16**, 166 (1930).
- (25) KIRCHOFF: Botan. Centr. **126**, 154 (1913), and many others.
- (26) KNUDSON: J. Biol. Chem. **14**, 159 (1913).
- (27) LÖWE: Z. anal. Chem. **13**, 46 (1874); **20**, 208 (1881).
- (28) MANNING AND NIERENSTEIN: J. Chem. Soc. **115**, 662 (1919).
- (29) MEYER AND SAUL: Ber. **26**, 1276 (1903).
- (30) MICHEL-DURAND: Rev. gén. botan. **40**, 705 (1928) and later papers.
- (31) NIERENSTEIN: Ber. **44**, 837 (1911).
- (32) NIERENSTEIN: The Natural Organic Tannins, p. 14. J. and A. Churchill, Ltd., London (1934).
- (33) Reference 32, p. 56.
- (34) Reference 33, p. 160 et seq.
- (35) NOMURA, HIROSHI: Bull. soc. chim. **37**, 1245 (1925).
- (36) OVERTON: Jahrb. wiss. Botan., p. 171 (1899).
- (37) PELOUZE: Ann. chim. phys. **57**, 423 (1834).
- (38) PERKIN, A. G.: J. Chem. Soc. **87**, 398 (1905).
- (39) PERKIN, A. G., AND COLLABORATORS: J. Chem. Soc. **70**, 1289, 1299, 1303 (1896); **71**, 1131, 1194 (1897); **73**, 374, 1016 (1898); **77**, 423 (1900).
- (40) PERKIN, A. G., AND COLLABORATORS: J. Chem. Soc. **87**, 1425 (1905); **89**, 251 (1906); **103**, 1194 (1908); **109**, 529 (1916) etc.
- (41) PERKIN AND EVEREST: The Natural Organic Colouring Matters, p. 413. Longmans, Green and Co., London (1918).

- (42) For early work on gallotannin see reference 41, p. 418 et seq.
- (43) Reference 41, p. 438.
- (44) Reference 41, p. 439, et seq.
- (45) Reference 41, p. 440.
- (46) Reference 41, p. 464.
- (47) Reference 41, p. 470.
- (49) PERKIN, A. G., AND HUMMEL, J. J.: J. Chem. Soc. **85**, 1459 (1904).
- (49) PERKIN, A. G., AND UYEDA, Y.: J. Chem. Soc. **121**, 66 (1922).
- (50) PFEIFFER, KALCKBRENNER, KUNZE, AND LEVIN: J. prakt. Chem. **119**, 109 (1928).
- (51) PICK: Botan. Centr. **16**, 281 (1883).
- (52) RICHTER: J. prakt. Chem. [2] **29**, 294 (1883).
- (53) For a full account of depsides see RUSSELL, A.: "Lichen Acids and Depsides"  
in Annual Reports on the Progress of Chemistry **30**, 217 (1933).
- (54) RUSSELL, A.: J. Chem. Soc. **1934**, 218.
- (55) RUSSELL, A., AND TODD, J.: J. Chem. Soc. **1934**, 1069.
- (56) Reference 55, p. 1506.
- (57) RUSSELL, A., TODD, J., AND WILSON, C. L.: J. Chem. Soc. **1934**, 1940.
- (58) RYAN, H., AND WALSH, M. J.: Sci. Proc. Roy. Dublin Soc. **15**, 113 (1916).
- (59) STRECKER: Ann. **90**, 340 (1854).
- (60) TRIMBLE: The Tannins. J. B. Lippincott Co., Philadelphia (1894).
- (61) VAN ESENBECK, NEES: Ann. **1**, 243 (1832).
- (62) VON KOSTANECKI AND LAMPE: Ber. **40**, 4910 (1907).
- (63) WIESNER: Botan. Z. **20**, 389 (1862).

# THE CHEMISTRY OF THE CARDIAC GLYCOSIDES

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## I. INTRODUCTION

Within the past few years our knowledge of the chemical structure of the more important cardiac glycosides has been developed to such an extent that it is now possible to bring order out of the confusion in which these substances have hitherto been enveloped. Strikingly enough, they are now



found to fall into the growing list of substances related to the sterols and bile acids, but the fact that this exact relationship has been demonstrated subsequent to the more recent reviews of the latter substances, taken together with the occurrence of several individual features characteristic of the cardiac drugs, would seem to warrant a somewhat fuller treatment of their chemistry independent of the sterol group.

The cardiac glycosides comprise a group of naturally occurring substances placed together because of their common characteristic action on the heart. The present treatment will be restricted to a discussion of their chemistry with but passing attention given to their physiological and pharmacological properties, a phase which has already been competently presented by Cushny (19). Suffice it to say that the pharmacological study of these substances had kept far ahead of the accumulation of strictly chemical information available. This was doubtless due to a variety of factors. The plants in which these materials occur not infrequently contain several active constituents which are responsible for the physiological action. The active principles, in addition to possessing at times very similar physical properties, often occur in relatively small amounts—a combination of circumstances which has rendered the isolation of chemical individuals exceedingly difficult. Furthermore, such substances are of a very complex structural character and often quite labile, so that their isolation in crystalline form has been hindered. In many cases where crystalline compounds have been reported, these have later been shown to be mixtures. The presence of relatively large quantities of saponins and other inert substances which are extracted along with the cardiac principles frequently alters the solubilities of the active substances, a circumstance which contributes in no small measure to the difficulty of their isolation.

## II. OCCURRENCE AND FORMULATION OF THE CARDIAC GLYCOSIDES

The use of infusions of certain plants for the treatment of cardiac diseases in medicine has been known to a number of peoples for centuries. However, until the latter part of the eighteenth century this use was based on purely empirical knowledge. The geographical distribution of plants containing cardiac principles is rather wide, many species being found in tropical regions where the principal use made of them seems to have been in the preparation of arrow and ordeal poisons. There also seems to be no rule governing their distribution in the vegetable kingdom for, while the majority of the plants appear to be included in the order of *Apocynaceae*, others have been found in the *Scrophulariaceae*, *Liliaceae*, and *Ranunculaceae*.

The classical review of Schmiedeberg (151) and the more recent treat-

ment of these substances by Jacobs (47) have described the better known glycosides of the group. However, inasmuch as new information has accumulated since the latter appeared, it will be necessary to treat this phase of the subject in some detail in order that the present discussion may be complete. With the exception of the toad venoms and the nitrogenous principle of *Erythrophloeum guineense*, the active principles are glycosides consisting entirely of carbon, hydrogen, and oxygen. The glycosides on treatment with acids are hydrolyzed more or less easily with formation of the component sugars and the non-carbohydrate constituents, termed the aglycones or "genins." The sugars so obtained have proved in a number of instances to contain certain unusual structural features. Several of them fall in the class of 2-deoxysugars, which fact renders the glycosides extremely labile and easily hydrolyzed. Others belong to the normal type of sugars with hydrolysis in consequence being more difficult, a circumstance which has occasioned difficulty in obtaining the aglycones without extensive alteration produced by the necessarily severe hydrolytic conditions. Tables 1 and 2 list the important members of the group.

#### A. *Digitalis glycosides*

*Digitalis purpurea*. In 1875 Withering published his epoch-making treatise on the therapeutic powers of the foxglove in the treatment of dropsy. Subsequent workers traced these effects to a specific and characteristic action on the heart, and as a result a large amount of work with this drug has been recorded which far exceeds that with any other cardiac drug. The search for the active principle in the early days proved so unfruitful that in order to stimulate activity La Société de Pharmacie de Paris in 1835 offered a prize of 500 francs for its isolation. Five years later this was increased to 1000 francs. In 1841 Homolle and Quevenne (43) isolated a highly active, partly crystalline mixture from the leaves of *Digitalis purpurea*, called by them "digitaline;" to this work was awarded the prize. This was apparently the first successful isolation of even a crude cardiac glycoside. Since then, work on this subject has been prolific.

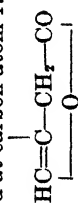
The seeds and especially the leaves of the plant have been the source of therapeutic preparations. The active glycosides preponderating in the former, while closely related to those in the latter, are substances distinctly different. Extraction of the seeds with water removes all the glycosides (162) and yields a complex mixture of active and inactive glycosides; one of the former has been recognized as a chemical individual, the digitalin of Schmiedeberg (150), who also noted its glycosidic nature. Kiliani (98), using commercial *Digitalinum pur. pulv. germanic* (Merck), obtained it practically pure, renamed it digitalinum verum, and developed a practical method of separating it from other substances (98). He also adopted a

TABLE 1  
*Cardiac glycosides of definitely determined structure*

GLYCOSIDE	FORMULA	FUNCTIONS AND POSITIONS IN THE AGLYCONES	SUGAR COMPONENTS	PRINCIPAL SOURCE
Digitoxin . . . . .	$C_{41}H_{64}O_{13}$	Normal side chain,* OH on carbon atoms 3 and 14; $CH_3$ on carbon atom 10	3 digitoxose	Leaves of <i>Digitalis purpurea</i>
Gitoxin . . . . .	$C_{41}H_{64}O_{14}$	Normal side chain; OH on carbon atoms 3, 14, and 16; $CH_3$ on carbon atom 10	3 digitoxose	Leaves of <i>Digitalis purpurea</i>
Purpurea glycoside A (de- acetyldigilanide A) . .	$C_{47}H_{74}O_{13}$	Same as digitoxin	3 digitoxose; 1 glucose	Leaves of <i>Digitalis purpurea</i>
Purpurea glycoside B (de- acetyldigilanide B) . .	$C_{47}H_{74}O_{13}$	Same as gitoxin	3 digitoxose; 1 glucose	Leaves of <i>Digitalis purpurea</i>
Digilanide A . . . . .	$C_{49}H_{76}O_{13}$	Same as digitoxin	3 digitoxose, one of which contains an acetyl group; 1 glucose	Leaves of <i>Digitalis lanata</i>
Digilanide B . . . . .	$C_{49}H_{76}O_{20}$	Same as gitoxin	3 digitoxose, one of which contains an acetyl group; 1 glucose	Leaves of <i>Digitalis lanata</i>

Cymarín.....	$C_{30}H_{48}O_8$	Normal side chain; OH on carbon atoms 3, 5, and 14; CHO on carbon atom 10	1 cymarose	Various species of <i>Apocynum</i> Enzymatic hydrolysis of certain strophanthus glycosides
Alloecymarín.....	$C_{30}H_{48}O_8$	Same as cymarín, but stereoisomeric	1 cymarose	Enzymatic isomerization of k-strophanthus glycosides
k-Strophanthín-β.....	$C_{30}H_{48}O_{14}$	Same as cymarín	Strophanthobiose (1 cymarose and 1 glucose)	k-Strophanthus seeds
Periplocymarín ....	$C_{30}H_{48}O_8$	Normal side chain; OH on carbon atoms 3, 5, and 14; CH <sub>3</sub> on carbon atom 10	1 cymarose	Wood and bark of <i>Periploca græca</i>

\* The normal side chain is considered to be attached at carbon atom 17, and to have the structure



All the aglycones have a CH<sub>3</sub> group on carbon atom 13.

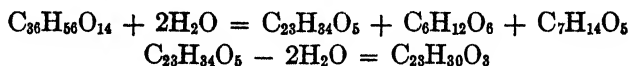
TABLE 2  
*Cardiac glycosides in which rigid proof for some particulars is still lacking*

GLYCOSIDE	FORMULA	FUNCTIONS AND POSITIONS IN THE AGLYCON	SUGAR COMPONENTS	PRINCIPAL SOURCE
Digitalinum verum ...	$C_{41}H_{64}O_{14}$	Normal side chain; OH on carbon atom 3; two double bonds from removal of two OH groups during hydrolysis;* $CH_3$ on carbon atom 10	1 digitalose; 1 glucose	Seeds of <i>Digitalis purpurea</i>
Digoxin.....	$C_{41}H_{64}O_{14}$	Presumably normal side chain; presumably OH on carbon atom 3; presumably $CH_3$ on carbon atom 10; two OH groups, position unknown	3 digitoxose	Leaves of <i>Digitalis lanata</i>
Digilanide C. ....	$C_{41}H_{64}O_{14}$	Same as digoxin	3 digitoxose, one of which contains an acetyl group; 1 glucose	Leaves of <i>Digitalis lanata</i>
Ouabain.....	$C_{27}H_{44}O_{11}$	Normal side chain; presumably OH on carbon atoms 3 and 14; three OH groups which are removed during hydrolysis;* substituent on carbon atom 10 may be $CH_2OH$	Rhamnose	Seeds of <i>Strophanthus gratus</i> Bark of ouabaio tree
Sarmentocynarin .....	$C_{41}H_{64}O_{14}$	Normal side chain; presumably OH group on carbon atoms 3 and 14; one OH group, position unknown; presumably $CH_3$ on carbon atom 10	Sarmentose	Seeds of <i>Strophanthus sarmentosus</i>

Oleandrin. ....	$C_{27}H_{44}O_{11}$	Same as digitalinum verum	Probably digitalose	<i>Nerium oleander</i>
Uzarin.....	$C_{27}H_{44}O_{11}$	Presumably normal side chain; OH group on carbon atom 3; two OH groups, position unknown, which are removed during hydrolysis;* $CH_3$ on carbon atom 10	2 glucose	Wood of <i>Uzara</i>
Scillaren A. . . . .	$C_{27}H_{44}O_{11}$	Side chain: $CH=C-CH=CH-CO$ <div style="text-align: center;"> <math>\begin{array}{c}   \\ \text{---} \text{O} \text{---} \end{array}</math> </div> attached to carbon atom 17; presumably OH group on carbon atom 14;* one OH group and one double bond, position not certain; $CH_3$ on carbon atom 10	1 rhamnose; 1 glucose	<i>Scilla maritima</i>
Proscillaridin A . . . . .	$C_{27}H_{44}O_{11}$	Same as scillaren A	1 rhamnose	Enzymatic hydrolysis of scillaren A

\* The aglycone has never been isolated as such, anhydro derivatives formed by loss of hydroxyl groups during the hydrolysis being obtained. Double bonds mentioned in this table are in addition to the side chain one.

formula,  $C_{36}H_{56}O_{14}$ , for the substance and showed that it yielded on hydrolysis an aglycone, digitaligenin, and two sugars, digitalose and glucose. More recent work of Windaus and coworkers (188) has shown that Kiliani's formula must be revised to  $C_{36}H_{56}O_{14}$ . Further, the digitaligenin of Kiliani is not the primary aglycone, but a dehydration product of the original aglycone,  $C_{23}H_{34}O_5$ , probably gitoxigenin, produced by removal of two molecules of water under the comparatively severe hydrolytic conditions necessary. Hence the hydrolysis of digitalinum verum is represented by:



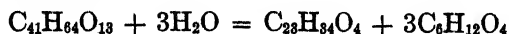
In digitalinum verum it appears likely that digitalose is the sugar joined directly to the aglycone, and that glucose is attached to one of the remaining hydroxyl groups of the digitalose molecule. This is suggested by the fact that crystalline oleandrin (to be treated later, p. 201) has been shown by Windaus and Westphal (196) to be a glycoside of an aglycone, probably gitoxigenin, and of a sugar, probably digitalose. Addition of a glucose molecule to oleandrin could possibly give digitalinum verum.

Little is known of other active glycosides of the seeds, which are undoubtedly present. Among them may be mentioned the digitalein of Schmiedeberg (150), a mixture concerning the chemistry of which nothing is known (110).

Turning to the leaves, one is confronted with a much more complicated picture. After a long period of confusion certain facts have emerged which can be regarded as definitely proved. Roughly two-thirds of the active glycosides can be extracted with water, the remainder by 50 per cent alcohol. From this extract two glycosides have been isolated in pure crystalline form by numerous workers,—digitoxin and gitoxin. A third glycoside, gitalinum cristallisatum, has been described by Cloetta.

Digitoxin occurs mainly in the alcoholic extract of the leaves after preliminary exhaustion with water, and it is isolated by careful fractionation of the material removed from this extract with ether. Digitoxin in a highly impure state was probably the substance in the hands of Homolle and Quevenne (43), as well as the main constituent of the original "digitoline cristallisée" of Nativelle (135), who apparently was the first to have isolated it in a state approaching purity. Schmiedeberg, in the course of a study of it, adopted the name digitoxin (150, 151). Arnaud (5) appears to have been the first to have prepared it in a high state of purity. He recognized its glycosidic character as well as the presence of a saponifiable group (lactone). Others who have investigated it are Kiliani (100), Krafft (117), and, more recently, Cloetta (17) and Windaus and coworkers (186, 191c). Kiliani showed that it is easily cleaved on acid hydrolysis to

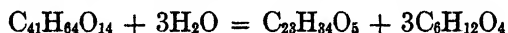
digitoxigenin and digitoxose. The correct formulation has been shown by Windaus (187) to be  $C_{41}H_{64}O_{13}$ , or digitoxigenin,  $C_{23}H_{34}O_4$ , joined in glycosidic union with three molecules of digitoxose. Its hydrolysis is represented by the following equation:



Only one of the digitoxose molecules can be directly joined to the aglycone.

Krafft (117) described a water-soluble glycoside, gitalin, extractable from the aqueous extract of the leaves by chloroform. This substance on heating in aqueous solution deposited a sparingly soluble, so-called dehydration product, "anhydrogitalin." Kiliani (109) showed gitalin to be a complex mixture of substances and, more recently, Windaus and Schwarte (194) and Cloetta (18) showed "anhydrogitalin" to be an impure form of a glycoside already present in the leaves, which is characterized by its very sparing solubility in alcohol and chloroform. It appears as the purification of the crude drug proceeds and is collected by taking advantage of its insolubility in chloroform.

The substance has been named gitoxin by Windaus and Schwarte (digitalinum cristallisatum by Cloetta). Windaus, Westphal, and Stein (197) derived the correct formula,  $C_{41}H_{64}O_{14}$ , and showed the substance to consist of an aglycone, gitoxigenin,  $C_{23}H_{34}O_5$ , joined to three molecules of digitoxose, which are readily obtained on acid hydrolysis:



On treatment with alcoholic hydrochloric acid, gitoxigenin readily loses two molecules of water with the formation of a dianhydro derivative identical with digitaligenin, the product of the hydrolysis of digitalinum verum.

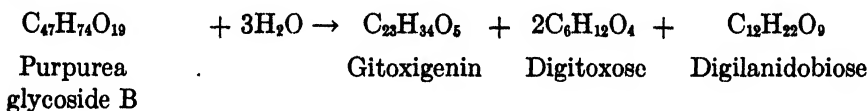
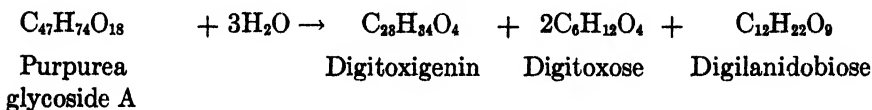
The gitalinum cristallisatum,  $C_{17}H_{28}O_6$ , of Cloetta (18) was reported to yield on hydrolysis one molecule of digitoxose and one molecule of a new aglycone, gitaligenin,  $C_{11}H_{18}O_3$ , the close relationship of which to gitoxigenin was apparent from its ready conversion into derivatives of the latter on acylation and dehydration. However, Cloetta's interpretation of gitalinum cristallisatum is open to question. Windaus (190) and Jacobs and Gustus (75a) have discussed this subject and have pointed out that titration of the lactone group indicated the molecular size of the genin to be of the same order of magnitude as that of the other genins. Windaus arrived at the conclusion that gitaligenin may be considered a hydrate of gitoxigenin, and that the glycoside has a formula in the neighborhood of  $C_{35}H_{56}O_{12} \cdot 0.5H_2O$ . This substance, however, is in need of reinvestigation.

Kiliani (101) reported another crystalline glycoside, which he at first considered to be a distinct substance and designated  $\beta$ -digitoxin. Later he



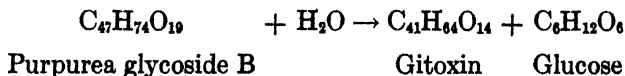
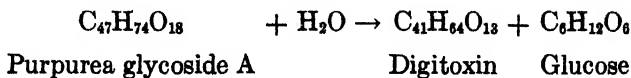
regarded it as identical with digitoxin. However, he claimed to have obtained on hydrolysis with stronger acid an aglycone derivative, so-called  $\beta$ -anhydrodigitoxigenin, which melted at 223°C., contrasting with ordinary anhydrodigitoxigenin for which melting points of 183°C. and 193°C. have been observed. No other report of such a substance has been recorded.

Very recently Stoll and Kreis (158), following the earlier work of Jacobs and Hoffmann (84) on the enzymatic cleavage of the *strophanthus* glycosides, have succeeded in isolating a new series of glycosides from the leaves of *Digitalis purpurea*. By a special technique of extraction whereby enzymatic cleavage is hindered, they have obtained two glycosides, corresponding to digitoxin and gitoxin, both of which however contain an additional glucose molecule, the so-called *purpurea* glycoside A (deacetyl-digilanide A first obtained from *Digitalis lanata*, to be discussed later) and *purpurea* glycoside B (deacetyldigilanide B). These on acid hydrolysis break in accordance with the following scheme:



Digilanidobiose on stronger hydrolytic treatment yields glucose, but the conditions used cause decomposition of the digitoxose component. Its presence has been proved indirectly by an enzymatic method.

If the glycosides be subjected to the action of an enzyme obtained from the leaves, their hydrolysis is represented as follows, and the nature of the second component of digilanidobiose is at once obvious.



*Digitalis lanata*. The chemistry of the glycosides contained in the leaves of this species has recently been the subject of investigation. The glycosides contained therein have been shown to be closely related to, and in some cases identical with, those occurring in *D. purpurea*. Smith (154) was the first to describe a new glycoside, digoxin, isomeric with gitoxin,  $\text{C}_{41}\text{H}_{64}\text{O}_{14}$ . On hydrolysis it yields digoxigenin,  $\text{C}_{23}\text{H}_{34}\text{O}_5$ , isomeric with

gitoxigenin, and three molecules of digitoxose. In addition, Smith also found gitoxin.

Mannich, Mohs, and Mauss (126) have reported four glycosides, the principal one of which is lanadigin,  $C_{41}H_{66}O_7$ , and which yielded on hydrolysis an aglycone,  $C_{23}H_{34}O_5$ , lanadigenin, identical with Smith's digoxigenin. The sugar fraction consisted of digitoxose and a disaccharide,  $C_{12}H_{22}O_9$ , which was more resistant to acids.

A second glycoside, called by them lanata glycoside II, yielded on hydrolysis two genins—digoxigenin and digitoxigenin—and as sugars, digitoxose and the above disaccharide. This glycoside maintained the appearance of chemical homogeneity in all attempts at fractional crystallization. However, in view of the later observations of Stoll and Kreis (159), who noted the strong tendency of these substances to form mixed crystals, it is not improbable that this substance may be a mixture. A third glycoside was considered to be digitalinum verum. Finally, the fourth glycoside, for which a formula of either  $C_{29}H_{48}O_{11}$  or  $C_{42}H_{66}O_{16}$  was given, gave on hydrolysis glucose and a genin, either  $C_{23}H_{32}O_3$  or  $C_{30}H_{42}O_4$ .

More recently Stoll and Kreis (159) have applied their technique of extraction to the leaves of this species. Three glycosides were thus obtained: digilanides A, B, and C with formulas  $C_{49}H_{76}O_{19}$ ,  $C_{49}H_{76}O_{20}$ , and  $C_{49}H_{76}O_{20}$ , respectively. Digilanide A is composed of one molecule of digitoxigenin, three molecules of digitoxose, and one molecule of glucose. In addition, an acetyl group is present, presumably attached to one of the digitoxose units. Enzymatic cleavage with digilanidase, from the leaves, removes the glucose to give acetyldigitoxin. Saponification of the acetyl group in this with calcium hydroxide gives digitoxin, which on acid hydrolysis behaves in the usual manner. Saponification of the acetyl group in the original digilanide A leads to deacetyldigilanide A, identical with the above-mentioned purpurea glycoside A. However, direct acid hydrolysis of digilanide A gives one molecule of digitoxigenin, two molecules of digitoxose, and one molecule of digilanidobiose apparently identical with Mannich's biose. Digilanide B is composed of one molecule of gitoxigenin, three molecules of digitoxose, one molecule of glucose, and one acetyl group; digilanide C is similar except that the aglycone, gitoxigenin, is replaced by digoxigenin. Both show exactly the same type of hydrolytic reactions as digilanide A. An interesting isomerization occurs under the influence of the enzyme, whereby two glucose-free acetylglycosides are formed. They are physiologically alike in their action, but show different optical properties. Apparently this change involves the arrangement of the acetyl group, since deacetylation gives the same deacetylglycosides from both isomers. In this connection the change is confined to the sugar portion of the molecule in contrast to the allomerization of strophanthidin, to be discussed later, which involves the aglycone.

*B. Apocynaceae*

*Strophanthins*. As previously mentioned, the *Apocynaceae* family embraces the largest number of plants containing cardiac poisons. The aborigines of Africa have made use of infusions of the seeds and bark of a number of species of *Strophanthus* in the preparation of arrow poisons. Chemical work on these substances has suffered in the past, owing to incompleteness of botanical data on the seeds from which the glycosides have been prepared. Inasmuch as some forty odd varieties of *Strophanthus* plants have been reported, confusion was almost inevitable. In time, clarification ensued as this difficulty was recognized, and certain easily accessible species were investigated. Thoms (169) made the suggestion that the first letter of the species from which the glycosides were obtained be prefixed to the term "strophanthin"—thus, k-strophanthin from *S. kombé*, h-strophanthin from *S. hispidus*, g-strophanthin from *S. gratus*, etc.

The *kombé* arrow poisons were the subject of classical studies by Fraser (30) and Arnaud (3). Subsequently Feist (29) reinvestigated them. However, the work of these investigators suffered from uncertainty as to the identity of the *Strophanthus* species under examination. They did succeed in showing the glycosidic character of the material from which an aglycone, strophanthidin, was obtained on hydrolysis. The critical reviews of Heffter and Sachs (40) and Brauns and Closson (10) accomplished much to clarify this subject. The former reported on identified *hispidus* seeds and commercial *kombé* seeds, while the latter studied identified *kombé* and commercial *hispidus* seeds. The identical aglycone, strophanthidin, was obtained by both workers from both varieties. *Kombé* seeds were found to yield two strophanthidin glycosides,—a crystalline k-strophanthin, sparingly soluble in water, and an amorphous, water-soluble k-strophanthin.

More recently, the glycosides of *S. kombé* have been given extensive study by Jacobs and Hoffmann. While practically all the glycosides are derivatives of one aglycone, strophanthidin, the nature of the sugar components has been found to vary, and it is certain that none of the glycosides in the hands of the earlier workers was an individual substance. Strophanthidin, as first shown by Jacobs and Heidelberger (80), has the formula  $C_{23}H_{32}O_6$ . The *kombé* strophanthins appear to be made up of one molecule of cymarín joined with one or more glucose units. Cymarín had previously been found in a number of varieties of *Apocynum* (*cannabinum*, *androsemifolium*, and *venetum*). It was first isolated by Taub and Fickewirth (24) and subsequently shown by Windaus and Hermanns (193) to possess the formula  $C_{30}H_{44}O_9$  and to yield strophanthidin and cymarose,  $C_7H_{14}O_4$ , on hydrolysis.

The so-called crystalline k-strophanthin of the earlier workers was found by Jacobs and Hoffmann (83) to be resolvable into two components, viz.

chloroform-soluble cymarín and chloroform-insoluble k-strophanthin- $\beta$ . The latter represents cymarín in combination with one additional glucose unit. On hydrolysis it gives strophanthidin and a biose, strophanthobiose,  $C_{13}H_{24}O_8$ , which requires such vigorous hydrolytic conditions for its further breaking down that decomposition of the resulting sugars ensues. However, in the *Strophanthus* seeds an enzyme, strophanthobiase, was found which possesses the property of hydrolyzing the union between the two monoses in k-strophanthin- $\beta$  with the formation of one molecule of cymarín and one molecule of glucose, thus demonstrating the nature of strophanthobiose.

By application of the enzyme method, the mixture of higher water-soluble glycosides, the so-called amorphous k-strophanthin, which predominates in the *kombé* seeds, has been broken down to cymarín. While the exact formulation of these glycosides is a matter of uncertainty, analyses of samples thereof have indicated that the chief component of the mixture is a trioside consisting of cymarín in union with two glucose molecules. However, the production of cymarín from all of them shows that strophanthidin is joined in glycosidic union only with cymarose.

A curious type of enzymatic isomerization of the k-strophanthus glycosides has been noticed by Jacobs (46). After digestion of a suspension of ground and defatted *S. kombé* seeds, which procedure had been attempted in the hope of going directly to the easily isolatable cymarín, the glycoside found proved to be not cymarín but an isomer, allocymarín. It yielded on hydrolysis cymarose and an aglycone, allostrophanthidin, which, while retaining all the functional groups of strophanthidin, nevertheless differed from the latter in its stereo configuration. Thus, there is a second enzyme present in the seeds in addition to strophanthobiase, which possesses the power of isomerizing the strophanthidin molecule while still in glycosidic union. In contrast to the isomerization noted by Stoll and Kreis (159) in the case of the acetyldigilanides, this allomerization involves the aglycone portion of the molecule and the typical cardiac action is almost, if not entirely, destroyed by the change.

*Strophanthus hispidus*. The glycosides of this species, while closely resembling those of *S. kombé*, nevertheless show certain differences. Jacobs and Hoffmann (87) obtained a complex mixture of water-soluble glycosides from the seeds, from which it was possible to obtain cymarín after enzymatic cleavage of glucose. However, the h-strophanthins differ from the k-strophanthins in being considerably more resistant to hydrolysis.

Very recently Tschesche (173) has reported the isolation of derivatives of two new aglycones from seeds which were considered to be *S. hispidus*. Without isolation of the glycosides he subjected the mixture obtained by methyl alcohol extraction of the seeds directly to hydrolytic cleavage by

acid. To the first of these,  $\alpha$ -monoanhydrohispidogenin-A, is ascribed the formula  $C_{23}H_{32}O_4$ . It is presumably derived from an aglycone,  $C_{23}H_{34}O_5$ , from which one hydroxyl group has apparently been removed as water during the hydrolysis. The second, dianhydrohispidogenin-B,  $C_{23}H_{30}O_6$ , is similarly derived from an aglycone,  $C_{23}H_{34}O_8$ , which loses two hydroxyl groups during the hydrolysis. Tschesche's results are definitely at variance with the experience of earlier workers, since from the seeds studied by him derivatives of aglycones other than strophanthidin were obtained.

*Strophanthus gratus*. The Pahouins have long made use of an arrow poison prepared from the seeds of this species. The principal glycosidic constituent thereof is ouabain, a material which possesses an unusually strong power of crystallization, thus rendering its isolation and purification comparatively simple. For this reason it has been used as a standard in the assay of commercial digitalis and strophanthus preparations. Arnaud (2) first discovered ouabain in the roots and bark of the ouabaio tree, a species of *Acocanthera* used as an arrow poison by the Somalis of East Africa. He assigned to it the formula  $C_{30}H_{46}O_{12}$ , showed it to be a rhamnose glycoside of an hypothetical aglycone,  $C_{23}H_{36}O_8$ , and noted the presence of a saponifiable group through the formation of a crystalline barium salt. Ouabain, in contrast to the easily hydrolyzable deoxysugar glycosides, shows such resistance to hydrolytic cleavage that under the conditions necessary, dehydration of the aglycone with possible polymerization ensues. As a result, the latter has never been isolated, and its chemistry has until recently remained obscure. Jacobs and Bigelow (50) revised Arnaud's formulas for ouabain and its aglycone to  $C_{23}H_{44}O_{12}$  and  $C_{23}H_{34}O_8$ , respectively. They have also succeeded in securing crystalline derivatives of the aglycone by the use of special procedures. These will be discussed later. *S. gratus* seeds also contain a mixture of amorphous glycosides concerning which nothing is known.

In addition to crystalline ouabain, several other crystalline or amorphous glycosides have been reported from various species of *Acocanthera*. Among these may be mentioned the rhamnose glycoside, acocantherin, of Fraser and Tillie (31) and Faust (28), to which the formula  $C_{32}H_{50}O_{12}$  has been assigned, and several arrow poisons such as the crystalline glucose glycoside ukambin of Paschkis (137), and the glycosides of the Wakamba arrow poison studied by Brieger (11). Some of these on further study may be found to be identical with, or closely related to, ouabain. For a detailed ethnological study of the arrow poisons the reader is referred to Lewin (123).

*Strophanthus sarmentosus*. Jacobs and Heidelberg (81) have investigated the glycosides obtained from *S. sarmentosus*. The seeds contain a mixture of glycosides, from which especially after the use of the enzymatic

method a crystalline substance, sarmentocymarin,  $C_{20}H_{46}O_8$ , was extracted with chloroform. The glycoside is easily hydrolyzed and yields an aglycone, sarmentogenin,  $C_{22}H_{34}O_5$ , and a sugar, sarmentose,  $C_7H_{14}O_4$ , which is isomeric with cymarose. The nature of the more complex water-soluble but chloroform-insoluble glycosides has also been explained by the enzyme method and shown to consist of sarmentocymarin united with one or more molecules of glucose.

*Strophanthus eminii*. Jacobs and Bigelow (48) have found the seeds of this species to yield a mixture of easily hydrolyzable and more stable glycosides. By extraction of the concentrate obtained by alcoholic extraction of the seeds, a chloroform-soluble monoside,  $C_{30}H_{46}O_9$ , was obtained. On hydrolysis, which required severe conditions, a trianhydro derivative,  $C_{23}H_{28}O_2$ , of an hypothetical aglycone,  $C_{23}H_{34}O_5$ , was obtained. This substance was isomeric with trianhydroperiplogenin, a fact which would seem to indicate that the aglycone is not periplogenin (to be discussed later). However, it is not excluded that periplogenin in glycosidic union might yield such a trianhydro derivative. The sugar of this monoside is a methyl ether sugar either identical or isomeric with digitalose. On mild hydrolysis of the chloroform-insoluble glycoside mixture, a mixture of aglycones was obtained which consisted of strophanthidin and periplogenin, which can be taken to indicate the presence of deoxysugar glycosides. In addition, the characteristic Keller-Kiliani test was also given by the crude glycoside mixture. From the mother liquors from this hydrolysis a bioside,  $C_{36}H_{56}O_{14}$ , was isolated. This probably consists of the above monoside with an additional hexose, possibly glucose, attached in a manner analogous to the conditions found in the case of k-strophanthin- $\beta$ . On hydrolysis it gave the same trianhydroaglycone as did the monoside.

*Nerium oleander*. This member of the family *Apocynaceae* is a plant the poisonous properties of which were known in antiquity, Hippocrates having recorded observations thereon. The leaves contain a mixture of glycosides, the chemistry of which was given a superficial study by Schmiedeberg (151) and by Pieszczyk (141). A crystalline oleandrin has been prepared in very poor yield from the leaves of the plant in the laboratories of C. F. Boehringer and Söhne at Mannheim-Waldhof. This was shown by Windaus and Westphal (196) to be a glycoside,  $C_{31}H_{46}O_9$ , which on hydrolysis yields digitaligenin and a sugar, probably digitalose. Its possible close relationship with digitalinum verum has already been noted (p. 194). In addition to crystalline oleandrin, a number of other glycosides, some crystalline and some amorphous, have been reported by Leulier (121), Tauber and Zellner (167), and Tanret (165). The chemistry of these is still obscure. *Nerium odorum* has been stated by Greenish (36) to yield

two amorphous glycosides, neriodorin and neriodorein, the latter of which is soluble in water. On hydrolysis a reducing sugar and a crystalline aglycone were obtained.

*Thevetia neriifolia*. The nuts of this plant, known as "be-still nuts," have long been used in the Malayan archipelago as one of the chief sources of arrow poisons. A beginning has recently been made on their chemistry. De Vry (23) and Blas (7) obtained a water-soluble glycoside to which was given the name thevetin. More recently Weitz and Boulay (178) corroborated the presence of thevetin, and Ayyar (6) succeeded in isolating a crystalline glycoside. Ghatak (35) has reported two crystalline glycosides, thevetin and thevetoxin. Chen and Chen (13) have subjected the nuts to careful reëxamination and fully characterized one cardiac glycoside, thevetin, to which the formula  $C_{29}H_{46}O_{13} \cdot 2H_2O$  has been given. The sugar component has not been determined, and the aglycone has been obtained only in amorphous form. Herrera (42) has described a crystalline glycoside, thevetosin, yielding glucose and an amorphous aglycone, obtained from *Thevetia ycotli*, the joyote of Mexico, a plant the medicinal properties of which were made use of by the ancient Aztecs.

*Miscellaneous Apocynaceae*. Various other members of the family have been reported to yield active glycosides. Among these may be mentioned tanghinine, a crystalline glycoside from the nuts of *Tanghinia Madagascariensis*, first isolated by Olivier and Henry (136). Arnaud (4) assigned to it the formula  $C_{27}H_{44}O_{10}$  or  $C_{27}H_{46}O_8$ , and noted the presence of a saponifiable group by the formation of a crystalline barium salt. His description of its properties as closely resembling digitoxin makes a revision of his formula for tanghinine seem desirable. Bowrey (9) has described two crystalline glycosides from the leaves and green tips of *Urechites suberecta*, a native of the West Indies. Urechitoxin, for which the formula  $C_{13}H_{20}O_6$ , or a multiple thereof, is proposed, yields on hydrolysis a crystalline aglycone, urechitotoxin, and reducing sugar. Urechitin,  $C_{23}H_{42}O_8$ , also yields a crystalline aglycone. In addition, a mixture of amorphous glycosides was found. These substances have also been studied by Minkiewicz (131). Various species of *Adenium* have been used as arrow poisons in Africa, some of which have been given study. Boehm (8) isolated a crystalline glycoside,  $(C_6H_5O_2)_n$ , echugin (or echujiin), from the milk sap of *Adenium boehmianum*. On hydrolysis glucose and a crystalline aglycone, echujetin, were obtained. Krausse (118) has described an amorphous glycoside from *Adenium coetaneum*, used as an arrow poison by the Watindigas, and Perrot and Leprince (139) attribute the poison used by the natives of the French Sudan to a glycoside,  $C_{20}H_{31}O_8$ , from *Adenium hongkel*. Plugge (142) confirmed the presence of a crystalline glycoside, cerberin, isolated by de Vry (21) from the seeds of *Cerbera odallam*, which closely resembles tanghinine

and thevetin in many respects. He assigned to it the formula  $C_{27}H_{40}O_8$ ; upon hydrolysis he obtained amorphous cerberetin and glucose. However, the chemistry of these substances requires careful and discreet reinvestigation.

### C. *Asclepiadaceae*

*Periplocin.* Lehmann (120) isolated a crystalline glycoside from the stems of *Periploca graeca*, to which he gave the name periplocin. He also showed its glycosidic nature by hydrolysis to an aglycone, periplogenin, and reducing sugar. However, this substance is but one of a mixture which occurs in the plant. Jacobs and Hoffmann (86) showed this mixture to contain a monoside, periplocymarin, which is present in relatively small quantities as such, being mostly in combination with one or more molecules of glucose. By digestion of the purified extract of the plant with strophanthobias, the crude mixture of glycosides can be hydrolyzed to glucose and periplocymarin, which can then be extracted from the complex mixture with toluene. Periplocymarin possesses the formula  $C_{30}H_{46}O_8$ , and on hydrolysis gives periplogenin and cymarose.

The water-soluble periplocin of Lehmann was probably a bioside consisting of periplogenin in combination with cymarose, which is in turn combined with glucose. Its formula, therefore, should perhaps be  $C_{36}H_{56}O_{13}$  and not  $C_{30}H_{46}O_{12}$ , as provisionally adopted by Lehmann at a time when the nature of the sugar component had not been determined.

*Uzarin.* In Africa certain tribes have made use of a species of *Gomphocarpus* called uzara, the root of which has furnished a drug "uzaron." Gürber (37) isolated a crystalline glycoside, uzarin, to which the drug owes its activity. Hennig (41) and Wolff (198) showed that it yielded a crystalline aglycone, uzarigenin, and glucose on hydrolysis. Windaus and Haack (192) assigned the formula  $C_{36}H_{56}O_{16}$  to uzarin and showed it to be a glycoside of a hypothetical aglycone,  $C_{23}H_{34}O_6$ , combined with two molecules of glucose. However, the conditions required for the hydrolysis of uzarin cause decomposition of the aglycone which, therefore, has not been isolated. The product obtained by Windaus and Haack was a dianhydrouzarigenin,  $C_{23}H_{30}O_8$ .

Karsten (95) has described an amorphous glycoside, dregein, from the seeds of *Dregea rubicunda*. It is very easily hydrolyzed to yield reducing sugar and a crystalline aglycone, which might indicate the presence of a deoxysugar. It resembles strophanthin very closely.

### D. *Liliaceae*

*Scilla maritima.* Following several previous investigators Stoll and coworkers (161) succeeded in isolating a crystalline glycoside—scillaren



A—from the bulbs of the squill. An excellent historical review of earlier work is given in Stoll's paper. Scillaren A has been assigned the formula  $C_{37}H_{54}O_{13}$ ; on direct acid hydrolysis it yields scillaridin A,  $C_{25}H_{32}O_8$ , and scillabiose,  $C_{12}H_{22}O_{16}$ , a rhamnose-glucose biose.<sup>1</sup> During the hydrolysis one molecule of water is removed from the aglycone, so that the scillaridin A obtained is in reality a dehydration product of a hypothetical genin,  $C_{25}H_{34}O_4$ , which has never been obtained as such. The nature of scillabiose has been determined by the enzymatic method similar to that used by Jacobs and Hoffmann in the investigation of the strophanthins. Scillarenase (160), present in the bulbs, hydrolyzes scillaren A to give glucose and proscillaridin A,  $C_{31}H_{44}O_8$ , which on acid hydrolysis gives rhamnose and scillaridin A. The amorphous squill glycosides, grouped under the name scillaren B, have not as yet been resolved into pure constituents. However, on hydrolysis of the mixture a small crystalline aglycone fraction was obtained—scillaridin B—to which the tentative formula  $C_{15}H_{18}O_3$  was given.

*Convallaria majalis*. From various parts of this plant highly active glycosides have been prepared. Walz (177) isolated a crystalline substance to which he gave the name convallarin. He recognized its glycosidic character and on its hydrolysis obtained a crystalline aglycone to which he assigned the formula  $C_{28}H_{52}O_6$ . However, it is quite certain that Walz's substance was a mixture. Tanret (164) obtained a crystalline glycoside, convallamarin, from the roots. On hydrolysis he obtained crystalline convallamaretin,  $C_{20}H_{36}O_8$ . Votacek and Vondracek (176) reported the sugars obtained by hydrolysis of convallamarin to be glucose, galactose, and a hexomethyllose, which were also obtained from convallarin. More recently Lindner (124), by fractional crystallization of Merck's commercial convallarin, obtained an amorphous glycoside which he regarded as uniform, to which he gave the formula  $C_{25}H_{38}O_9$ . On hydrolysis it gave crystalline convallaretin,  $C_{19}H_{28}O_4$ , and a sugar, probably glucose. In a later paper (125) the isolation of three different amorphous glycosides from Merck's convallarin was reported. Jacobs and Hoffmann (85) isolated from the roots a crude, highly active, amorphous substance which, however, did not give the nitroprusside reaction. Finally, Karrer (94) isolated from the flowers a highly active crystalline glycoside, convallatoxin, which appeared to be different from any of those previously reported. It is definitely placed in the category of the cardiac glycosides by giving a positive nitroprusside reaction. A negative Keller-Kiliani test indi-

<sup>1</sup> In view of the recent conversion of scillaridin A into allocholanic acid by Stoll, Hoffmann, and Helfenstein (155), a revision of the formulas for scillaren A to  $C_{39}H_{58}O_{13}$ , for proscillaridin A to  $C_{33}H_{46}O_8$ , and for scillaridin A to  $C_{24}H_{30}O_3$  is strongly indicated.

cated that it was not a glycoside of a deoxysugar. The compounds previously reported should be accepted with caution until a thorough reinvestigation of the convallaria glycosides is made.

### *E. Ranunculaceae*

*Adonis vernalis*. An extract of this plant has been used since the time of Hieronymus Tragus as a remedy in various ailments of the heart. Cervello (12) isolated an amorphous glycoside to which he gave the name adonidin. Mordagne (133) obtained the substance in a partly crystalline form. Fuckelmann (33) in an exhaustive investigation isolated two amorphous glycosides, the so-called neutral adonidin and adonidinic acid. Both gave a Keller-Kiliani test indicating the presence of deoxysugars. Fromherz (32) corroborated Fuckelmann and definitely placed the glycosides in the digitaloid category by observing a positive nitroprusside reaction. Mercier and Mercier (128, 129) in an extensive study confirmed Fuckelmann's adonidin and renamed it adonidoside. However, they concluded that his adonidinic acid was a mixture of a new glycoside, adonivernoside, and an acid decomposition product of the latter. The two glycosides were separated by taking advantage of the relative solubility of adonidoside in water. Thus the existence of two glycosides in *Adonis vernalis* seems to have been definitely demonstrated. No crystalline aglycone has been obtained from either.

Kromer (119) obtained from *Adonis aestivalis* a glycoside which showed many similarities to adonidin. He named it adonin and suggested the formula  $C_{25}H_{40}O_{10}$ . On hydrolysis, which was accomplished by a mere trace of acid, an amorphous aglycone and glucose were obtained. However, it would appear likely that in view of the easy hydrolysis, plus the positive Keller-Kiliani test, a deoxysugar may be a part of the molecule. Kiefer (97) has also investigated adonin.

Tahara (163) and Inoko (45) have described a glycoside obtained from *Adonis amurensis*, which appeared from pharmacological data to be different from the previously reported adonidin or adonin. Analysis indicated a formula  $C_{24}H_{40}O_9$  and the ease of hydrolysis was again noted.

*Helleborus species*. Infusions of hellebore have been used in medicine since the time of Hippocrates. Despite this, the chemistry of the active principle remains obscure. Von Huseman and Marmé (44) isolated from the roots of *Helleborus niger*, *H. viridis*, and *H. foetidus* two glycosides, helleborein and helleborin. However, helleborein was subsequently shown to be responsible for the cardiac action, while helleborin possessed only the usual hemolytic properties of saponins. They assigned to helleborein the formula  $C_{26}H_{44}O_{15}$ . On hydrolysis of helleborein they obtained an amorphous aglycone, helleboretin,  $C_{14}H_{20}O_3$ , and two molecules of a

hexose, probably glucose. Thaeter (168) obtained helleborein in the crystalline state, revised the formula to  $C_{37}H_{66}O_{18}$ , and upon hydrolysis obtained amorphous helleboretin,  $C_{19}H_{30}O_5$ , two molecules of glucose, and three molecules of acetic acid. Keller (96) confirmed the presence of both glycosides, and Delattre (20) confirmed Thaeter's formulation. Sieburg (153) made a more exhaustive study of the substance. He readjusted the formula to  $[C_{19}H_{31}O_5 \cdot OOCCH_3]_3$ . On hydrolysis his products were glucose, arabinose, acetic acid, and two amorphous aglycones,—an acid helleboretin, derived perhaps by saponification of a labile lactone during manipulation, and a neutral helleboretin,  $C_{15}H_{24}O_3$ . He made the further interesting observation that in addition to its digitaloid properties, helleborein also possesses weak saponin-like characteristics. Thus, it is weakly hemolytic and shows a tendency to foam in solution and to be precipitated by cholesterol.

From the *Anemone hepatica*, another *Ranunculacea*, Delattre (20) has reported a crystalline glycoside. However, nothing is known of its composition.

#### F. Miscellaneous species

In the East Indies there grows the stately upas tree, or *Antiaris toxicaria*, of the family *Moraceae*, which towers above its neighbors, and which has long been held in awe by the natives because of the poisonous properties of its sap. The latter is the chief constituent of the Ipooch arrow poison. Pelletier and Caventou (138) gave the material a superficial study, and Mulder (134) isolated the active principle in crystalline form and named it antiarin. De Vry and Ludwig recognized its glycosidic character (22). Later Kiliani (99) in a series of studies reported the isolation of two crystalline glycosides,  $\alpha$ - and  $\beta$ -antiarin, to both of which he assigned the formula  $C_{27}H_{40}O_{10}$ . On hydrolysis both yielded in small amounts the same crystalline aglycone, antiarigenin, to which Kiliani gave the formula  $C_{21}H_{28}O_6$ . The sugar component of the two was found to be different. Neither sugar is a deoxyhexose, which accounts for the small yield of aglycone.  $\beta$ -Anti-arin yielded rhamnose, and the  $\alpha$ -glycoside gave an isomer of rhamnose, antiarose. However, it seems probable that when a more careful investigation of antiarin can be performed, the formulas of the glycosides and genin will require revision.

Schlagdenhauffen and Reeb (148) isolated an amorphous glycoside, coronillin ( $C_7H_{12}O_5$ )<sub>n</sub>, from the seeds of *Coronilla scorpioides*, *C. glauca*, and *C. montana* of the family of *Leguminosae*. On hydrolysis, glucose and an amorphous coronilléine ( $C_8H_{12}O_7$ )<sub>n</sub> were obtained. Tanret (166) obtained the same glycoside and reported that it gave a positive Keller-Kiliani test, but upon hydrolysis he obtained only glucose and an amorphous genin.

He suggested the formulas  $C_{23}H_{33}O_{10}$  and  $C_{17}H_{23}O_6$  for the glycoside and genin, respectively. Hydrolysis with *Aspergillus niger* gave a crystalline aglycone,  $C_{14}H_{18}O_3$ , and glucose.

Two members of the *Celastraceae* family have yielded active glycosides. Plugge (143) obtained a crystalline glycosidic substance, rabelaisin, from *Rabelaisia philippinensis*. Prescott (145) confirmed Wenzell's isolation of an amorphous glycoside from the root of *Euonymus atropurpurea* (179). Rogerson (147) failed to obtain the glycoside but did get a crystalline substance,  $C_{21}H_{30}O_4$ , which possessed an intensely bitter taste and gave a positive Liebermann-Burchard reaction. In the aqueous mother liquors from this, glucose was found. This might be taken to suggest that Rogerson's substance was in reality the aglycone, particularly in view of the rather drastic conditions to which he subjected the crude extract which might have caused hydrolysis of the glycoside.

A glycoside reported to possess both hemolytic and digitaloid properties is the mowrin isolated from the seeds of *Bassia longifolia* of the *Sapotaceae* family (132). It was given the formula  $C_{61}H_{84}O_{32}$ ; on hydrolysis it gave glucose and amorphous mowric acid.

### III. THE AGLYCONES

The structures of strophanthidin, periplogenin, digitoxigenin, and gitoxigenin have been determined with a reasonable degree of certainty. A beginning has been made in the study of scillaridin A and the toad venoms. Inasmuch as the latter substances show some differences from the four former ones, they will be treated separately. The structure of uzarigenin is known except for the positions occupied by two of the hydroxyl groups, the two which are removed during the hydrolysis of uzarin. The structures of the remaining members of the group are at present unknown, although it is probably safe to predict that, in general, they will be found to conform to the same pattern as those which have been studied in detail.

Certain structural features are common to the members of the strophanthidin group of aglycones and are highly characteristic of these substances. These will be discussed first, then the ring system will be treated, and finally the characteristic features of the individual aglycones will be taken up.

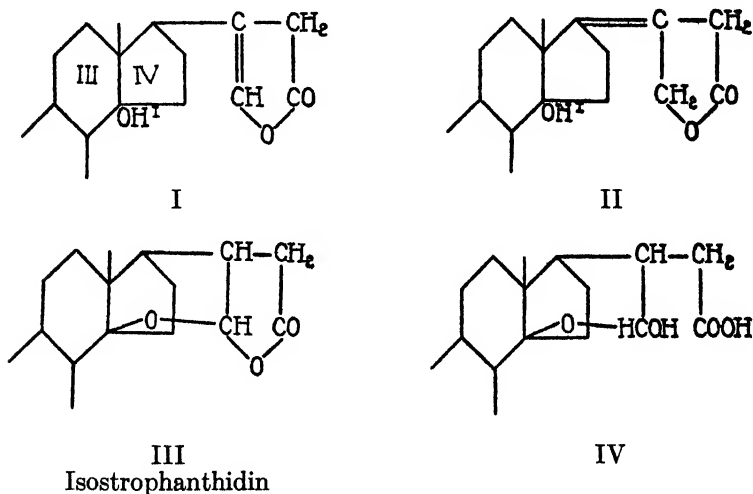
#### A. The lactone group

The presence of a saponifiable group in certain of the aglycones was first noted by Arnaud (2, 4, 5). He succeeded in isolating crystalline barium salts after saponification of digitoxin, ouabain, and tanghinine, and considered that an anhydride was present in the molecule. Feist (29) showed

the saponifiable group to be a lactone. The more recent investigations of Jacobs and coworkers have demonstrated that the lactone consists of a side chain of four carbon atoms which constitutes the most characteristic portion of the molecule. The double bond (the only ethylenic unsaturation in the aglycones aside from that produced by secondary cleavage of hydroxyl groups during hydrolysis of certain glycosides such as ouabain and uzarin) is found in this side chain. This double bond can be catalytically reduced to form the dihydroaglycones. The whole side chain can be directly oxidized to a carboxyl group with loss of three carbon atoms in trianhydrostrophanthidin, and in certain other derivatives by a more indirect process. Moreover, the intensity of the physiological activity of the glycosides appears to depend to a large extent on the presence of this unsaturated side chain (117, 191b). Many of the typical reactions of the aglycones, such as the production of a red color with alkaline nitroprusside solution (the Legal reaction), reduction of Tollen's reagent, and the presence of an "active" hydrogen as shown by the Zerewitinoff test, have been shown to be conditioned by the presence of this unsaturated lactone side chain (82). These properties are all characteristics of  $\Delta^{\beta,\gamma}$  unsaturated lactones; they vanish in the dihydroderivatives, which also display a marked diminution in physiological activity.

The nature of this side chain has been shown to be that of a lactone of an enolized  $\gamma$ -aldehyde acid attached by its  $\beta$ -carbon atom to the main tetracyclic ring system. This has been elucidated by the results of a study by Jacobs and coworkers of the influence of alkali on the aglycones whereby the highly characteristic isoaglycones are formed. Isostrophanthidin will be taken as typical for the present discussion. When strophanthidin is dissolved in alcoholic alkali and the solution, after standing, acidified, an isomeric substance, isostrophanthidin, is produced (29, 54, 193). This compound, while still possessing a lactone group, no longer gives the Legal reaction, nor can it be catalytically hydrogenated. Furthermore, dihydrostrophanthidin does not undergo this change, hence the isomerization must be conditioned by the presence of the double bond. The explanation of the nature of the transformation to isostrophanthidin furnished the key to the interrelationship of the lactone group, the double bond, and one of the hydroxyl groups of strophanthidin. This is shown in formulas I to III. The change is not due to liberation of the free aldehyde group on saponification of strophanthidin followed by subsequent lactal formation, since preliminary saponification is not necessary in order that the strophanthidin-isostrophanthidin change may occur. Rather the explanation would seem to lie in a rearrangement involving a shift of the double bond. By assuming that in the original aglycone the unsaturated lactone side chain is *trans* to the hydroxyl group involved in the new oxidic bridge ( $\text{OH}^1$ ) (I), a shift of the  $\Delta^{\beta,\gamma}$  double bond to the position shown in formula II would

permit a *cis* rearrangement with consequent formation of the new oxidic bridge as shown in formula III. The new oxidic bridge involving OH<sup>I</sup> restricts the position of the latter group to one either  $\gamma$  or  $\delta$  to the enolized aldehyde group of strophanthidin. As will be shown later, the  $\delta$ -oxidic structure is preferable. After saponification of the lactone group of isostrophanthidin, the hydroxyaldehyde may exist in either the lactal (formula IV) or free aldehydic form. The existence of a free aldehyde group in saponified isostrophanthidin has been directly demonstrated by the formation of a semicarbazone in the case of an appropriate derivative of isostrophanthidin (70). A derivative of isodigitoxigenin has also yielded a similar semicarbazone (73). The lactal character of saponified isostrophanthidin (IV) is clearly demonstrated by its oxidation, with consumption of one atom of oxygen, to a new lactone as in  $\alpha$ -isostrophanthidin.



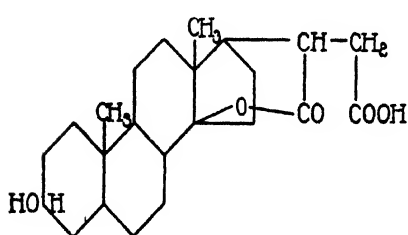
thidic acid (70). Further, the existence of the hydroxyaldehyde in both the free aldehydic and lactal forms is strikingly shown by the selective action of permanganate and hypobromite. The former acts specifically on the aldehyde group, whereas the latter oxidizes the lactal directly to the lactone (70).

Complementing these observations, oxidative degradation of the side chain, which will be treated in detail later, definitely fixed the number of carbon atoms comprising it.

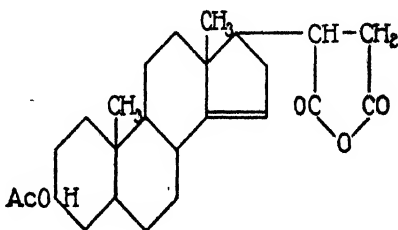
### B. The ring system

Although the view has often been expressed by workers in the field that the cardiac aglycones are closely related to the sterols and bile acids, until very recently there has been no direct proof for such a statement, beyond

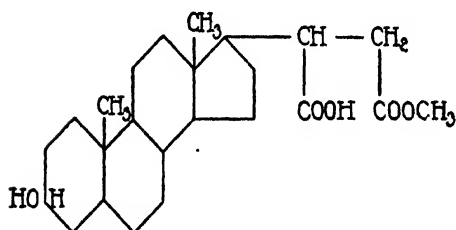
the fact that they are, like the sterols, reduced tetracyclic compounds. However, a direct relationship has now been demonstrated. The first evidence corroborating this view was forthcoming in the production of Diels' hydrocarbon (methylcyclopentenophenanthrene) upon dehydrogenation of strophanthidin (26) and of dianhydrouzarigenin (174) with



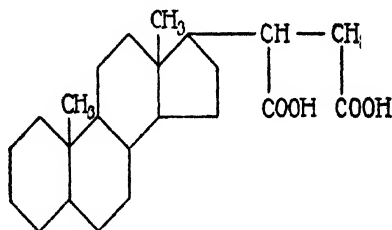
V  
Isodigitoxigenic Acid



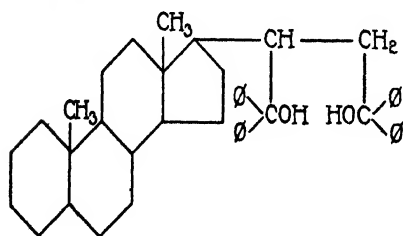
VI



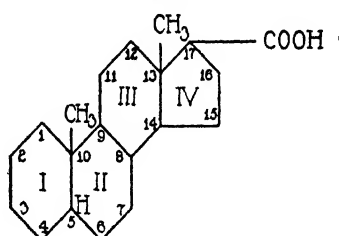
VII  
Digitoxanoldiacid methyl ester



VIII  
Digitoxandiacid



IX



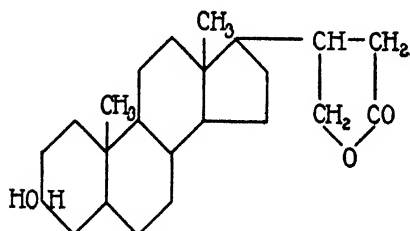
X  
Etiocholanolic acid

selenium. This compound has come to be regarded as a product characteristic of the sterols when they are subjected to the dehydrogenating action of selenium. Thus, it was indicated that, barring pyrolytic rearrangements during the course of the dehydrogenation, the two groups of substances did possess a common skeleton.

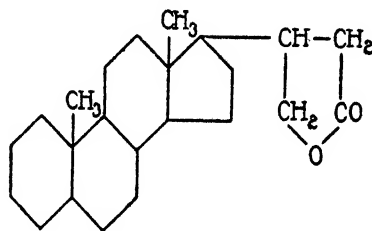
More recently a more direct proof has been provided—one which in

addition to furnishing decisive evidence on this point, also proved the point of attachment of the lactone side chain of the aglycone.

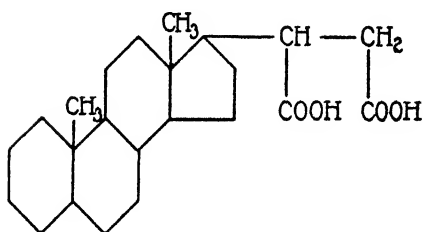
Jacobs and Elderfield (65) degraded a derivative of digitoxigenin to a saturated acid,  $C_{20}H_{32}O_2$ , which proved to be identical with etiocholanolic acid as obtained by a similar degradation of the side chain of cholanolic acid by Wieland, Schlichting, and Jacobi (184). The series of steps involved was as follows: Isodigitoxigenic acid (V) on treatment with acetic anhydride-acetyl chloride suffers cleavage of the lactone and removal of water, together with acetylation of the secondary hydroxyl group to yield the acetate of digitoxenoldiacid anhydride (VI) (77). This on saponification yielded digitoxenoldiacid, which as the half-ester was hydrogenated to



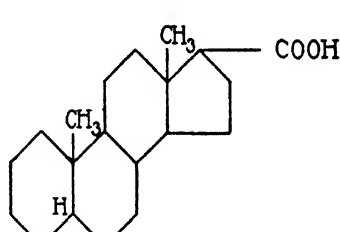
XI



XII



XIII



XIV

digitoxanoldiacid monomethyl ester (VII). After saponification of the ester group of the latter the remaining secondary hydroxyl group was then removed by oxidation to the ketone and reduction by Clemmensen's method giving digitoxandiacid (VIII) (65). The dimethyl ester of this acid was then degraded with loss of three carbon atoms of the side chain via the bis-diphenyl carbinol (IX), using the method of Wieland, Schlichting, and Jacobi (184), to yield a monobasic acid,  $C_{20}H_{32}O_2$  (X), identical with etiocholanolic acid.

A similar degradation of a fully hydrogenated derivative of dianhydro-uzarigenin was simultaneously carried out independently by Tschesche (171). Starting with one of the isomeric saturated lactones (XI) obtained



by hydrogenation of dianhydrouzarigenin, the remaining secondary hydroxyl group was replaced by hydrogen to yield the deoxylactone (XII). This on vigorous oxidation with chromic acid gave a dibasic acid (XIII) which, on degradation by the method used in the case of digitoxandiacid, led to an acid  $C_{20}H_{32}O_2$  (XIV). This acid, however, proved not to be etiocholanic acid but was identical with the spatially inverted isomer thereof, alloetiocholanic acid, which Tschesche prepared by degradation of the side chain of hyodeoxycholic acid (172).

Thus, independent proof was forthcoming from both laboratories not only of the conclusion that the carbon skeleton of the cardiac aglycones is identical with that of the sterols and bile acids, but also that the lactone side chain of the former is a fragment of the side chain of the latter and is attached to the skeleton at the same point, namely carbon atom 17.

Having established the ring system of the aglycones and the nature of the unsaturated lactone side chain, the individual characteristics of the various aglycones and their interrelationships will be discussed. In this connection, references will be given to communications in which the original observations were made, although it must be borne in mind that as the formulation of the aglycones underwent modification as additional evidence accumulated, such observations have of necessity undergone some reinterpretation (65).

### *C. Strophanthidin*

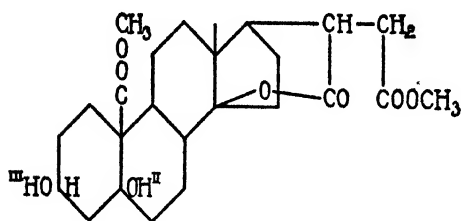
In addition to the lactone side chain, strophanthidin contains three hydroxyl groups and a carbonyl group. The carbonyl group has been shown to be in the form of an aldehyde, since oxidation with permanganate leads to the formation of an acid without degradation or ring cleavage but with disappearance of the carbonyl function (57). Of the hydroxyls, one ( $OH^{III}$ ) has been shown to be secondary through the formation of a monoketone on oxidation with chromic acid (72). The remaining hydroxyl groups are tertiary.

One of the two tertiary hydroxyl groups ( $OH^I$ ) must be involved in the strophanthidin-isostrophanthidin change, since appropriate derivatives of isostrophanthidin on oxidation still yield monoketones and hence retain the secondary hydroxyl group (70). This tertiary hydroxyl group must, in addition, be either  $\gamma$  or  $\delta$  to the enolized aldehyde group concerned in the unsaturated lactone side chain in order to account for the formation of the lactals and lactones characteristic of the isostrophanthidin series. These conditions restrict the position occupied by this hydroxyl group to carbon atom 14.

The remaining tertiary hydroxyl group ( $OH^{II}$ ) must bear a 1:3 relationship to the secondary hydroxyl group ( $OH^{III}$ ) for the following reasons.

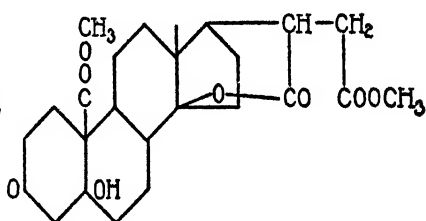
$\alpha$ -Isostrophanthic dimethyl ester (XV) on oxidation with chromic acid gives a ketone,  $\alpha$ -isostrophanthonic dimethyl ester (XVI), by oxidation of  $\text{OH}^{\text{III}}$  to carbonyl. In the latter compound  $\text{OH}^{\text{II}}$  has now become very labile and is easily removed as water (70), a property characteristic of  $\beta$ -hydroxyketones, to give anhydroisostrophanthonic ester (XVII). This demonstrates the relative positions of the two hydroxyl groups.

There remain to be proved the exact positions occupied by the aldehyde group,  $\text{OH}^{\text{II}}$ , and  $\text{OH}^{\text{III}}$ . The aldehyde group must be quaternary, for, as will be discussed later, (p. 217), it corresponds to one of the quaternary methyl groups of the sterols and other aglycones. This restricts its position to carbon atom 10 or 13. Carbon atom 13 is rendered improbable by

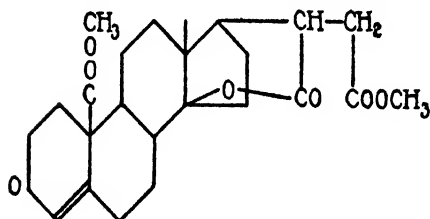


XV

$\alpha$ -Isostrophanthic dimethyl ester

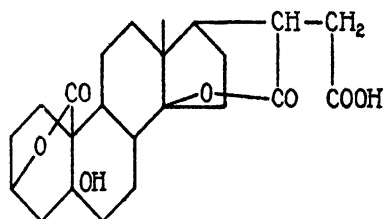


XVI



XVII

Anhydroisostrophanthonic dimethyl ester



XVIII

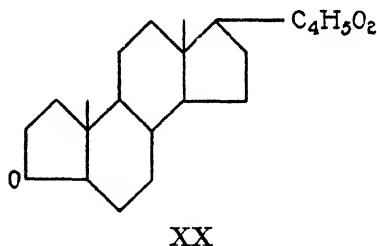
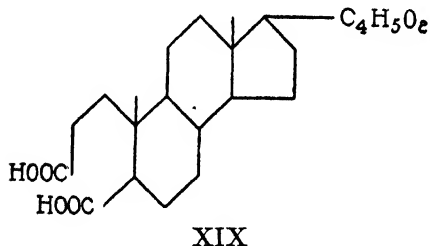
the observation, to be discussed at length later (p. 230), that in certain derivatives the aldehyde group, or carboxyl group derived from it on oxidation, is capable of undergoing lactal or lactone formation with  $\text{OH}^{\text{I}}$  (71) which has been placed definitely on carbon atom 14. Such lactals or lactones would then be  $\beta$  ones, a highly improbable arrangement. The alternative position, carbon atom 10, therefore remains as the point of attachment of the aldehyde group, which conclusion was substantiated by the following evidence.

The aldehyde group in  $\beta$ -isostrophanthidic acid, an isomer of the  $\alpha$  substance of the same name which will be treated later (p. 216), is capable of existing as a lactal involving the secondary hydroxyl group,  $\text{OH}^{\text{III}}$  (71).

This lactal on oxidation leads to a lactone (XVIII). That  $\text{OH}^{\text{III}}$  is involved in this lactone is shown by its failure to give a ketone on oxidation. From this it follows that the aldehyde group must be in reactive proximity to  $\text{OH}^{\text{III}}$ , i.e., either  $\gamma$  or  $\delta$ .

The final evidence needed definitely to place the aldehyde group,  $\text{OH}^{\text{II}}$ , and  $\text{OH}^{\text{III}}$  was supplied as follows. In a derivative of dihydrogitoxigenin (hexahydrodigitaligenin), wherein the hydroxyl groups have all been replaced by hydrogen save the secondary  $\text{OH}^{\text{III}}$  (which is common to all the aglycones), rupture of the ring bearing this hydroxyl group leads to a dibasic acid (XIX) (197). On pyrolysis of this acid a ketone (XX) was obtained which, in the light of the observations of Wieland and Dane (181) on the applicability of Blanc's rule to condensed ring systems, renders probable the fixing of  $\text{OH}^{\text{III}}$  on ring I.

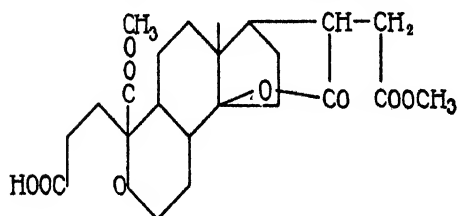
This assumption was confirmed and  $\text{OH}^{\text{III}}$  definitely located on carbon atom 3 by the following series of reactions. Anhydroisostrophanthonic dimethyl ester (XVII) on ozonization suffers rupture of ring I with loss of a carbon atom in a manner similar to that obtaining in the oxidation of



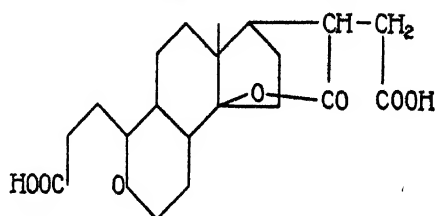
cholestenone, and a keto acid (undephanthontriacid) dimethyl ester (XXI) results (74). The latter, on being subjected to the action of weak alkali, undergoes the ketone decomposition of the  $\beta$ -ketonic ester group to give duodephanthondiacid (XXII). The latter on treatment with acetic anhydride-acetyl chloride is lactonized with the formation of the unsaturated lactone (XXIII) (79). Simultaneously, the isolactone on the other side of the molecule is cleaved, a change characteristic of the isoaglycone series (76). On catalytic hydrogenation, the unsaturated lactone is reduced to the saturated deoxyacid which, on saponification of the anhydride, gives dephanthanic acid (XXIV). This as the trimethyl ester, when subjected to the Wieland degradation over the trisdiphenylcarbinol (XXV), is degraded to dephanthic acid (XXVI) with the loss of four carbon atoms, three of which are accounted for by removal of the lactone side chain and the fourth by shortening of the side chain representing the fragment of ring I (64).

This series of reactions at once shows the presence of three consecutive secondary carbon atoms in the order  $-\text{CH}_2-\text{CHOH}-\text{CH}_2-$ , which

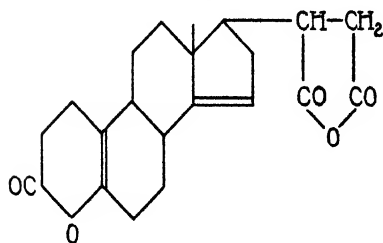
restricts the ring bearing  $\text{OH}^{\text{III}}$  to a terminal ring, ring I. It further follows that  $\text{OH}^{\text{III}}$  must be on carbon atom 3 and that  $\text{OH}^{\text{II}}$ , in order to be tertiary and in the  $\beta$ -position to  $\text{OH}^{\text{III}}$ , must be located on carbon atom



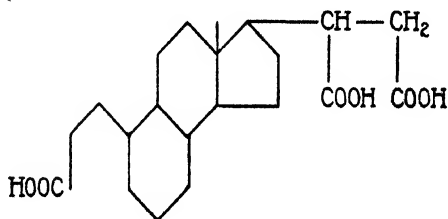
XXI  
Undephanthotriacid dimethyl  
ester



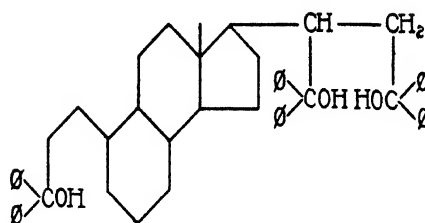
XXII  
Duodephanthondiacid



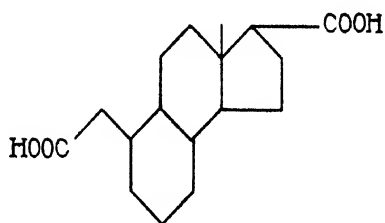
XXIII



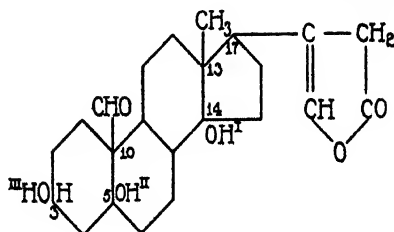
XXIV  
Dephanthanic acid



XXV



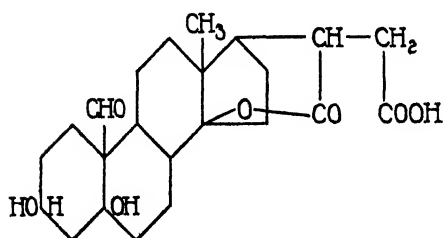
XXVI  
Dephanthic acid



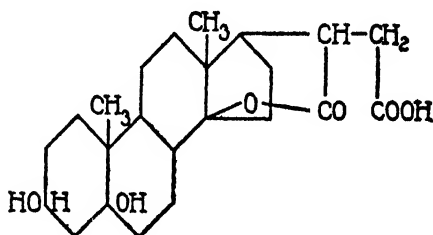
XXVII  
Strophanthidin

5. These conclusions as to the relative positions of the aldehyde group and the hydroxyl groups have been confirmed by a study of the hydroxy acids formed by the use of the cyanohydrin reaction on the aldehyde group of dihydrostrophanthidin and its anhydro derivatives (67). In these acids the new carboxyl group no longer reacts with  $\text{OH}^{\text{I}}$  or  $\text{OH}^{\text{III}}$  but does lactonize on  $\text{OH}^{\text{II}}$  to which it is now  $\gamma$ . Strophanthidin therefore possesses the structure shown in formula XXVII.

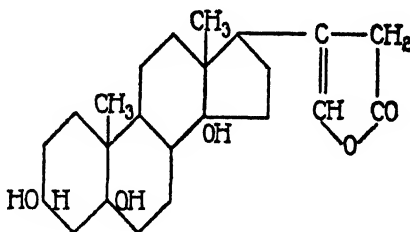
In discussing the positions occupied by the substituent groups in the other aglycones, it will be profitable to consider at the same time their interrelationships and transformations from one to another.



XXVIII  
 $\alpha$ -Isostrophanthidic acid



XXIX  
Isoperiplogenic acid



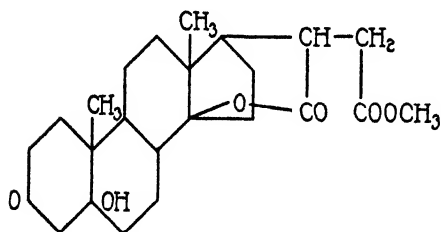
XXX  
Periplogenin

#### D. Periplogenin

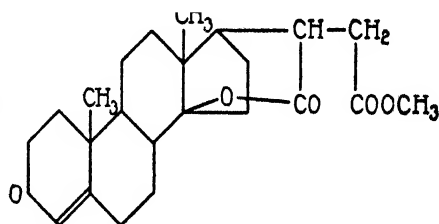
Jacobs and Elderfield (58) have correlated this aglycone with strophanthidin.  $\alpha$ -Isostrophanthidic acid (XXVIII), on conversion into the semicarbazone and reduction of the latter by the Wolff-Kishner method, yields a substance wherein the aldehyde group has been replaced by methyl (XXIX). This substance is identical with isoperiplogenic acid, from which it at once follows that periplogenin differs from strophanthidin only in having a methyl group in place of the aldehyde group of the latter. The hydroxyl groups being in the same positions in both aglycones, periplogenin is represented by formula XXX.

*E. Digitoxigenin*

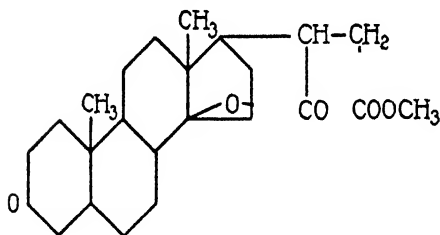
The same workers have also demonstrated the exact relationship of this aglycone to periplogenin and therefore to strophanthidin (59). Isoperiplogenic acid (XXIX), as the methyl ester, on oxidation with chromic acid yields isoperiplogonic methyl ester (XXXI). In the latter, as in the case of the analogous isostrophanthonic ester,  $\text{OH}^{11}$  has become labile and is easily split out, giving anhydroisoperiplogonic methyl ester (XXXII). This substance on catalytic hydrogenation gives a mixture of stereoisomers, one of which is identical with isodigitoxigonic methyl ester (XXXIII), the corresponding derivative of digitoxigenin. Digitoxigenin therefore is represented by formula XXXIV and differs from periplogenin in lacking  $\text{OH}^{11}$ .



XXXI

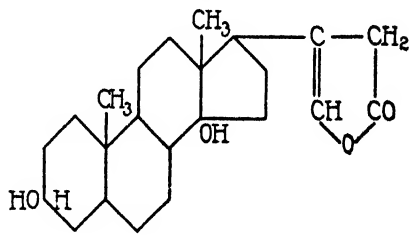


XXXII



XXXIII

Isodigitoxigonic methyl ester



XXXIV

Digitoxigenin

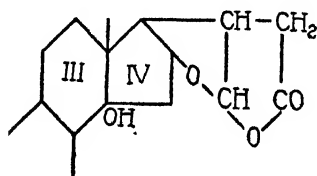
Inasmuch as digitoxigenin was converted into etiocholic acid by degradation of the side chain (65), it follows from these interrelationships that the aldehyde group of strophanthidin occupies the position of one of the quaternary methyl groups of cholic acid and specifically, as has been shown, this is carbon atom 10.

*F. Gitoxigenin*

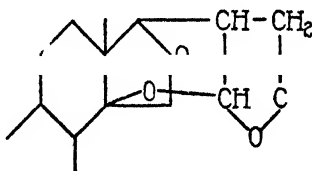
In some respects gitoxigenin shows certain divergences in its reactions from the three above-mentioned aglycones. These differences concern dihydrogitoxigenin and isogitoxigenin in particular.

Gitoxigenin is a trioxylactone, isomeric with periplogenin but differing from the latter in the position and character of one of the hydroxyl groups. This hydroxyl group is tertiary in periplogenin but secondary in gitoxigenin, as shown by the formation of a diketone, gitoxigenone, on oxidation. Both genins contain the secondary hydroxyl group ( $\text{OH}^{111}$ ). The position to be assigned to the extra secondary hydroxyl group of gitoxigenin has been determined from a study of isogitoxigenin by Jacobs and Gustus (75) and of dihydrogitoxigenin by Jacobs and Elderfield (63).

When gitoxigenin is dissolved in alcoholic alkali and then reacidified, an iso compound is formed which differs in several respects from the usual isogenins, such as isostrophanthidin, isoperiplogenin, and isodigitoxigenin. Contrasting with these substances, it does not react with the usual aldehyde reagents after saponification of the lactone group. The lactal is unusually stable. After oxidation with hypobromite to isogitoxigenic acid, the lactone group of the latter substance is relatively resistant to hydrolysis in contrast to the behavior of the corresponding derivatives of the other



XXXV



XXXVI

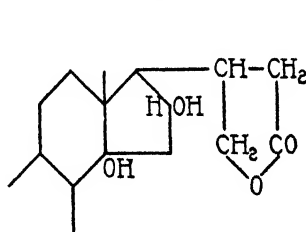
isogenins. The cause for this anomalous behavior lies in the fact that in the formation of isogitoxigenin the tertiary hydroxyl group which enters into the new oxidic ring in the other isoaglycones does not so function in this case. Instead, the extra secondary hydroxyl group of gitoxigenin is involved, as shown by the fact that isogitoxigenin gives only a monoketone on oxidation. This observation restricts the position of this secondary hydroxyl group to one of reactive proximity ( $\gamma$  or  $\delta$ ) to the enolized aldehyde group of the side chain.

However, when gitoxigenin is oxidized with chromic acid, the resulting diketone, gitoxigenone, no longer gives the Legal reaction. Oxidation experiments showed it to be a true isoaglycone wherein the tertiary hydroxyl group is involved in the new oxidic ring. This observation restricts the position of this hydroxyl group also to one of reactive proximity to the enolized aldehyde group of the side chain. These facts find expression in formula XXXV for isogitoxigenin and formula XXXVI for gitoxigenone.

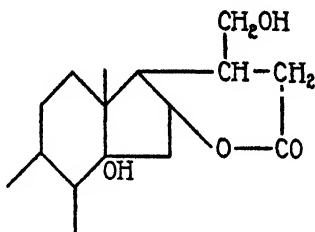
In view of the relationship of gitoxigenin to digitoxigenin, it appears better to designate gitoxigenone as oxoisodigitoxigenone. The rearrange-

ment involved in the formation of isogitoxigenin parallels that accompanying the formation of the other isoaglycones and apparently is due to the same factor, viz., a shift of the double bond of the side chain under the influence of alkali so that the side chain becomes *cis* to the hydroxyl group on carbon atom 16. In the case of oxoisodigitoxigenone, the presence of a carbonyl group on carbon atom 16 can also induce a similar shift of the double bond to a position  $\alpha, \beta$  to the new carbonyl group with rearrangement as above to a *cis* configuration and consequent formation of the new oxidic linkage.

The results of a study of the hydrogenation of gitoxigenin confirm this interpretation. Cloetta (18) noted that gitoxigenin is hydrogenated to two substances, which Windaus, Westphal, and Stein (197) showed to be isomeric dihydrogitoxigenins. The nature of their isomerization was explained by Jacobs and Elderfield (63). Both dihydrogitoxigenins show mutarotation during which they are mutually interconvertible, a fact which suggested a rearrangement involving the lactone group. This view was



XXXVII



XXXVIII

substantiated by the preparation of two isomeric dihydrogitoxigenin diacetates, neither of which exhibits mutarotation and which are not mutually interconvertible. It follows from this that in the isomerization of the normal  $\alpha$ -dihydrogitoxigenin to the  $\beta$  form, the lactone bridge has shifted to the secondary hydroxyl group, as shown in formulas XXXVII and XXXVIII, respectively.

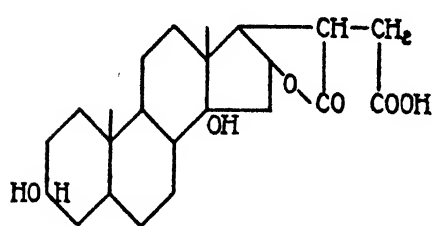
The placing of the tertiary hydroxyl group in a position 1:3 to the secondary one was confirmed by the behavior of the dihydrogitoxigenone derived from  $\alpha$ -dihydrogitoxigenin. This substance exhibited the properties of a  $\beta$ -hydroxyketone, the tertiary hydroxyl group having become labile and easily removed as water.

The correlation of gitoxigenin with digitoxigenin, while involving some difficulties, was accomplished by Jacobs and Gustus (77). Windaus and coworkers (191) had previously attempted to show the relationship between the two aglycones. Their procedure consisted in replacement of all of the hydroxyl groups, except  $\text{OH}^{\text{III}}$ , of both genins by hydrogen and

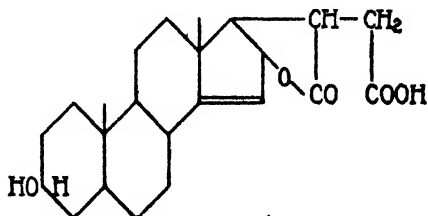


comparison of the fully saturated lactones thus obtained. However, the two lactones proved to be isomeric and not identical.

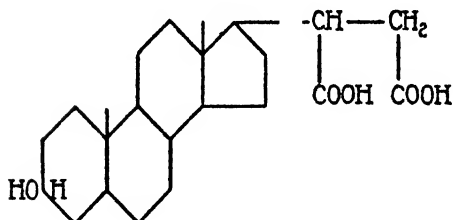
The former workers started with isogitoxigenic acid (XXXIX). On treatment with hydrochloric acid, the tertiary hydroxyl group of this substance was replaced by chlorine, which was then removed by alcoholic alkali to give an unsaturated hydroxylactone acid (XL). On catalytic hydrogenation of this substance, in addition to saturation of the double bond, the lactone group was opened to the saturated deoxyacid (XLI). The dimethyl ester of this acid proved to be identical with that obtained from the previously discussed digitoxanoldiacid (VII). Thus it was proved



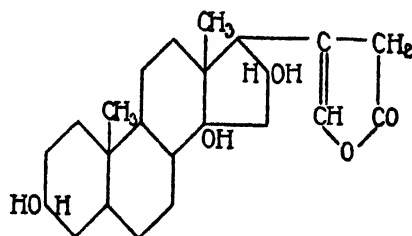
XXXIX  
Isogitoxigenic acid



XL



XLI



XLII  
Gitoxigenin

that gitoxigenin is hydroxydigitoxigenin, and further, that the secondary hydroxyl group on carbon atom 3 is common to both aglycones. Gitoxigenin is therefore represented by formula XLII.

#### G. Uzarigenin

As has already been noted, the substance obtained on hydrolysis of uzarin is a dianhydro derivative of the aglycone. Because of this fact, the positions occupied by the hydroxyl groups are not definitely known, with the exception of a secondary hydroxyl group on carbon atom 3. This hydroxyl group is the one retained in dianhydrouzarigenin, and its likely allocation on carbon atom 3 has been demonstrated by Tschesche (170). On oxidative cleavage of hexahydrodianhydrouzarigenin a ring at the

hydroxyl group in question is opened to give a dibasic acid. This on pyrolysis gives a pyroketone with loss of a carbon atom in a manner paralleling the reactions of hexahydrodigitaligenin.

Dianhydrouzarigenin has also been correlated with periplogenin by Tschesche (170). One of the isomeric hexahydrodianhydrouzarigenins on replacement of the remaining hydroxyl group by hydrogen gave the so-called fully saturated " $\alpha_2$  lactone." This was identical with the corresponding fully saturated lactone, octahydrotrianhydroperiplogenin, prepared by Jacobs and Bigelow (52).

There is also evidence suggesting that uzarin contains an hydroxyl group on carbon atom 5. This is indicated by the production of etiocholanolic acid from digitoxigenin, an aglycone which is unsubstituted at carbon atom 5, contrasting with the formation of alloetiocholanolic acid by a similar degradation of hexahydrodianhydrouzarigenin. This may indicate that in uzarin one of the hydroxyl groups which is removed during the hydrolysis of the glycoside is on carbon atom 5. On hydrogenation of the double bond thus produced, addition to this carbon atom may occur in such a way as to lead to the spatially inverted isomer of etiocholanolic acid. However, this type of evidence is far from conclusive since, as will be discussed later (p. 223), extensive wandering of double bonds occurs in the anhydroaglycones.

### *H. Ouabagenin*

As previously noted, ouabain is a rhamnose glycoside and as such, in contrast to the glycosides of the deoxysugars, requires such severe hydrolytic treatment as to cause dehydration and decomposition of the aglycone. Consequently the aglycone has never been isolated as such. However, Jacobs and Bigelow (50) by use of a special technique have succeeded in isolating derivatives of the aglycone. Arnaud (2) described an anhydroheptaacetate of ouabain obtained by the action of acetic anhydride and zinc chloride. This substance contains two double bonds in addition to the side chain one, as shown by its hydrogenation to deoxydihydroouabain heptaacetate (50). The latter compound on acetolysis led to a crystalline cleavage product,  $C_{24}H_{30}O_4$ , which, on the basis of saponification and hydrogenation experiments, was shown to be the monoacetate of a trianhydrolactone. However, the acetyl-free substance was a  $C_{22}$  compound instead of the expected  $C_{23}$  derivative which would bring it into conformity with the other  $C_{23}$  genins. An explanation for this discrepancy was found when formaldehyde was isolated from the acetolysis mother liquors. It is quite probable that ouabain contains a primary alcoholic group, on carbon atom 10 or 13, corresponding to one of the quaternary methyl groups of the sterols, and that during the acetolysis this carbon atom is lost as formaldehyde.

In another study, Jacobs and Bigelow (51) have further shown the close similarity between ouabain and the other glycosides. Ouabain as the glycoside is isomerized to an iso compound under the influence of alkali with disappearance of the Legal reaction. Attempts to hydrolyze this compound again resulted in the decomposition of the aglycone. However, when acetylation of isoouabain with acetic anhydride in the presence of a trace of sulfuric acid was attempted, the glycosidic linkage was cleaved, a carbon atom was lost as formaldehyde as in the acetolysis of the above heptaacetate, three molecules of water were lost, and the monoacetate of a trianhydrohydroxylactone resulted. The acetyl group was easily removed on saponification to give a hydroxylactone,  $C_{22}H_{26}O_4$ , but the three double bonds were resistant to catalytic hydrogenation, thereby suggesting a benzenoid arrangement as in the case of trianhydrostrophanthidin (to be discussed later, p. 224).

On saponification of the trianhydrohydroxylactone an acid was isolated as the methyl ester,  $C_{23}H_{30}O_5$ . The presence of a lactal as well as a secondary hydroxyl group in this substance was shown by its oxidation with chromic acid to a ketolactone ester. This paralleled the experience with the other isoaglycones. The hydroxyl group which emerged from the acetolysis reaction was also shown to be secondary and presumably identical with  $OH^{III}$  of strophanthidin and related aglycones.

Unfortunately, a more exact correlation of the aglycone of ouabain with other members of the group has not been accomplished, owing to its degradation to a  $C_{22}$  derivative during removal of the sugar component.

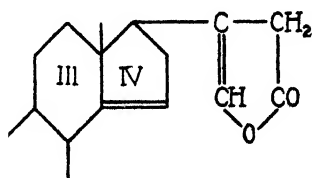
### *I. Anhydro derivatives of the cardiac aglycones*

When strophanthidin is allowed to stand in alcoholic hydrogen chloride solution, a sparingly soluble dehydration product separates. This was shown by Jacobs and Collins (53) to be the ethyl half-acetal of monoanhydrostrophanthidin. Under the influence of the reagent the aldehyde group of strophanthidin forms an internal cyclic acetal with  $OH^{III}$  in a manner analogous to the formation of simple glycosides of the sugars. Hydrolysis with dilute acid removes the ethylal group, giving the hydroxy-aldehyde which exists in either the free aldehydic or lactal form. The identity of the hydroxyl group ( $OH^I$ ), which is removed, was shown by the failure of monoanhydrostrophanthidin to yield an iso compound of the usual type under the influence of alkali.

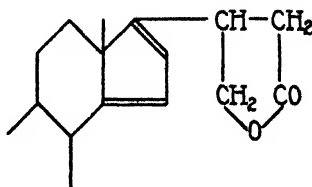
However, the ethylal of monoanhydrostrophanthidin when saponified with alkali leads to an aldehydo acid, the nature of which was shown by the formation of an oxime (56). On reacidification, the ethylal is hydrolyzed, and, in addition, lactonization occurs, not, however, with the reformation of monoanhydrostrophanthidin, but with the formation of an

isomeric substance which no longer gives the Legal reaction (66). The nature of this isomerization is explained by a shift of the  $\Delta^{\beta,\gamma}$ -lactone double bond from its original position in monoanhydrostrophanthidin (XLIII) to a position, conjugate with the new double bond arising from loss of  $\text{OH}^I$ , which would then permit relactonization to occur in the formation of isomonoanhydrostrophanthidin (XLIV or XLV).

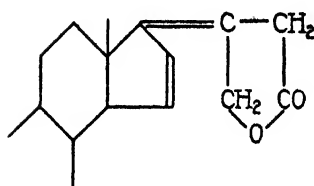
When monoanhydrostrophanthidin or strophanthidin itself is boiled with alcoholic hydrogen chloride, the ethylal of dianhydrostrophanthidin results. This compound arises from loss of both  $\text{OH}^I$  and  $\text{OH}^{II}$ . In its reactions it resembles very closely the monoanhydro derivative, except in its behavior after saponification of the lactone group. The aldehydo acid



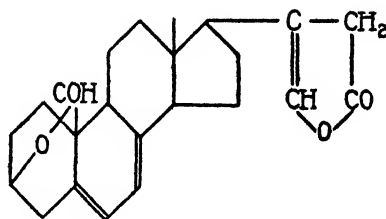
XLIII



XLIV



XLV



XLVI

thus obtained shows no tendency to relactonize. The explanation for this behavior apparently lies in the fact that the double bond formed by loss of  $\text{OH}^I$  in this case shifts to ring II in conjugation with that arising from loss of  $\text{OH}^{II}$  (formula XLVI). Influences tending to cause a shift of the side chain double bond are thus removed, and nothing is present which would facilitate relactonization of the lactone group when once opened.

The double bonds of both monoanhydro- and dianhydro-strophanthidin can be catalytically hydrogenated, that of the side chain being the last to be reduced (55). On oxidation of either of the anhydrostrophanthidins or of their reduced products, the lactal between the aldehyde group and  $\text{OH}^{III}$  is oxidized to a lactone, with the formation of dilactones. The unsaturated dilactones can be hydrogenated to the saturated ones, but the predominating stereoisomer obtained by this method is different from the

one which is obtained by reduction of the double bonds and subsequent oxidation of the lactal to the lactone (68). On exhaustive hydrogenation dianhydrostrophanthidin suffers reduction of the lactal to an alkylene oxide in addition to saturation of the double bonds. The same substance (octahydrotrianhydrostrophanthidin) is also obtained by Clemmensen reduction of hexahydrodianhydrostrophanthidin.

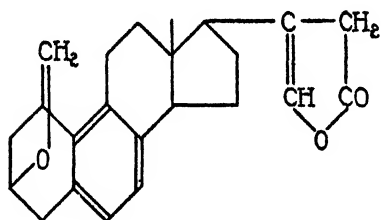
Upon treatment with concentrated hydrochloric acid, dianhydrostrophanthidin loses a third molecule of water and trianhydrostrophanthidin results (55). The formation of this substance is accompanied by loss of both the aldehydic and hydroxyl functions remaining in the dianhydrostrophanthidin molecule. This third molecule of water thus is apparently lost by dehydration of the lactal form of dianhydrostrophanthidin, with the formation of an alkylene oxide. At the same time, trianhydrostrophanthidin manifests several properties in striking contrast to those of its precursors. Whereas both monoanhydro- and dianhydro-strophanthidin can be completely catalytically reduced, the double bonds of trianhydrostrophanthidin (with the exception of the original  $\Delta^{\beta,\gamma}$ -lactone double bond) have resisted all attempts at catalytic hydrogenation. Trianhydrostrophanthidin does not add bromine to its double bonds as do its precursors, and on oxidation with permanganate in acetone, in contrast to dianhydrostrophanthidin, it suffers degradation of the lactone side chain with loss of three carbon atoms to a monobasic acid (69). On oxidation with chromic acid, a ring is opened with the formation, without degradation, of a dilactone acid. All of these reactions strongly indicated the presence of a benzenoid ring in trianhydrostrophanthidin, a fact which was confirmed by its ultra-violet absorption spectrum (25) and more recently by the production of benzenetetracarboxylic acid from it on oxidation with nitric acid (175).

The characteristic reactions of trianhydrostrophanthidin, which were studied rather early in the work on the aglycones, were largely the cause of misconceptions regarding their structure. For the logical deduction that oxidation of a side chain in an aromatic compound to a carboxyl group indicated attachment of such a side chain to an aromatic ring led to the placing of the lactone side chain of strophanthidin on a six-membered ring. Furthermore, a glance at the sterol skeleton with its two quaternary carbon atoms shows that the formation of a benzenoid ring in such a skeleton without rearrangement is impossible, and there had been no evidence of a rearrangement noted in the formation of trianhydrostrophanthidin. However, the direct correlation of digitoxigenin with cholic acid has made necessary a revision of the earlier ideas regarding trianhydrostrophanthidin. But one explanation is satisfactory—namely, that during its formation a sort of retropinacone rearrangement has occurred wherein the quaternary

aldehyde group attached to carbon atom 10 wanders to carbon atom 1 (66, 175). There is some evidence suggesting that this rearrangement has already occurred during the formation of monoanhydro- or dianhydrostrophanthidin.

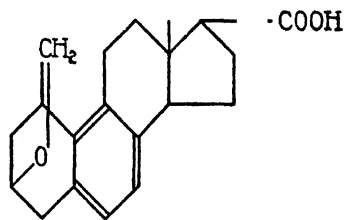
The structure of trianhydrostrophanthidin, therefore, is represented by formula XLVII; and the products obtained by oxidation of it with permanganate and chromic acid, by formulas XLVIII and XLIX, respectively. Other degradation products of trianhydrostrophanthidin have been described by Jacobs and Elderfield (66).

Dihydrostrophanthidin differs from strophanthidin in the lability of  $\text{OH}^I$ , the formation of a monoanhydro derivative of the former proceeding

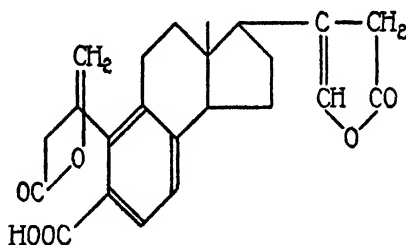


XLVII

Trianhydrostrophanthidin



XLVIII



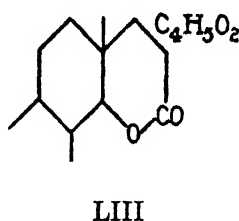
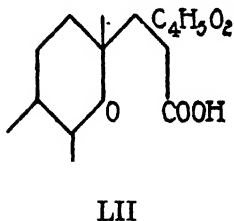
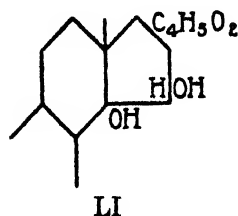
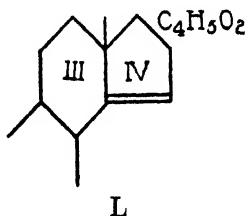
XLIX

with greater ease than in the case of the latter (85). A study of monoanhydrodihydrostrophanthidin (L) has been made by Jacobs and Elderfield (61). Alkaline permanganate oxidizes the aldehyde group to carboxyl, and simultaneously two hydroxyl groups are added to the double bond to give hydroxydihydrostrophanthidinic acid (LI). This substance as the methyl ester, on oxidation with chromic acid, suffers rupture of a ring with formation of a keto acid (LII),  $\text{OH}^{III}$  simultaneously being oxidized to a ketone. On catalytic reduction both ketone groups are reduced, and the hydroxy acid thus formed spontaneously lactonizes as the reduction proceeds (LIII). This easy lactonization, which presumably must involve either a  $\gamma$ - or  $\delta$ -lactone, at once showed the position occupied

by the double bond in monoanhydrodihydrostrophanthidin under these conditions, inasmuch as ring IV is the only ring which can be opened to give a keto acid leading to a  $\delta$ -lactone on reduction.

At the same time, it might be said that by the formation of a carboxyl group on carbon atom 15 in the above keto acid, independent proof was furnished of the presence of a  $\text{CH}_2$  group at that point of the sterol skeleton, and also of the point of attachment of the side chain.

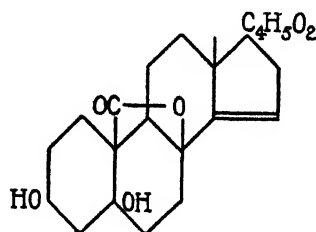
In another investigation, evidence has been obtained that in neutral or acid solution the double bond of monoanhydrodihydrostrophanthidin may also occupy the position between carbon atoms 8 and 14 (67). Oxidation of monoanhydrodihydrostrophanthidin in chloroform solution with per-



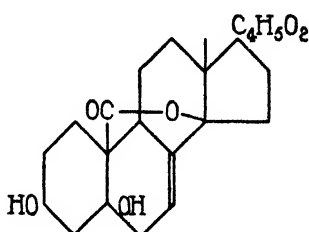
benzoic acid or with permanganate in acetic acid solution results in the formation of an ethylene oxide on the double bond. On hydration of this oxide, the resulting glycol promptly loses water in a variety of ways, depending on the form in which the aldehyde carbon atom happens to be. If the latter has been oxidized to a carboxyl group before opening the oxide, treatment with very weak acid (50 per cent acetic acid) gives an anhydrolactone (either LIV or LV), wherein the carboxyl group lactonizes on one of the new hydroxyl groups and the other new hydroxyl group is removed with formation of a double bond. But if the aldehyde group be reduced to  $\text{CH}_2\text{OH}$ , then opening of the ethylene oxide leads to the formation of a new oxidic linkage (LVI or LVII), involving one of the new hydroxyl groups and that derived from reduction of the aldehyde group. These reactions are in strong contrast to those displayed by

hydroxydihydrostrophanthidinic acid (LI), which is unusually stable towards dehydrating or lactonizing agents.

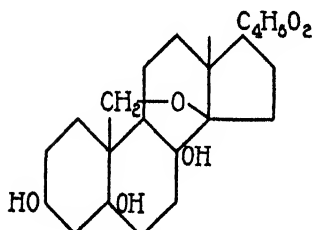
Other anhydro derivatives of strophanthidin have been studied. Of these, one formed by a reaction characteristic of the iso series has already been mentioned.  $\beta$ -Isostrophanthic lactone acid (LVIII) (to be discussed later, p. 229) on treatment with acetic anhydride-acetyl chloride



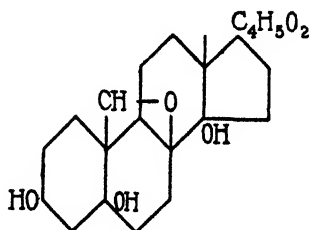
LIV



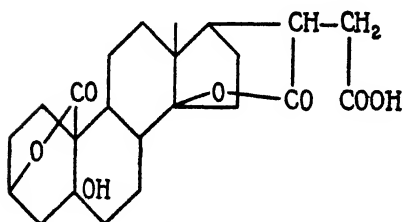
LV



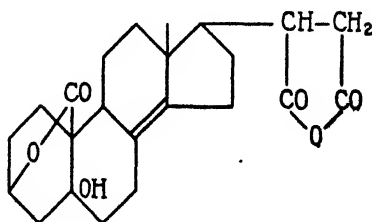
LVI



LVII



LVIII



LIX

undergoes cleavage of one of the lactone rings with the formation of an unsaturated anhydride (LIX) (76). The double bond in this substance apparently occupies the same position as that occurring in monoanhydrodihydrostrophanthidin, at least in acid solution, since an ethylene oxide was obtained which exhibited the same behavior, after hydration. The double bond in the anhydroanhydride can be catalytically hydrogenated.

By the action of methyl alcoholic hydrogen chloride on  $\beta$ -isostrophanthic lactone acid, the isolactone is similarly cleaved, and an unsaturated di-



methyl lactone ester is obtained corresponding to the above unsaturated anhydride. It, however, is not identical with the similar unsaturated dimethyl ester prepared from the acetic anhydride-acetyl chloride product. Besides differing sterically from the former substances, the double bond apparently lies in another position, since it cannot be catalytically hydrogenated.

Dihydrodigitoxigenin readily forms an anhydro compound which, on oxidation with alkaline permanganate, behaves in a manner analogous to the corresponding dihydrostrophanthidin derivative (62). With perbenzoic acid or permanganate in acetic acid, an ethylene oxide is formed, but all attempts at opening the latter have led to non-crystalline products.

Mention has already been made of the dianhydro derivative of gitoxigenin, digitaligenin, which results from the hydrolysis of digitalinum verum, or from the action of acid on gitoxigenin itself. In this substance only the hydroxyl group on carbon atom 3 remains. The tendency for gitoxigenin or dihydrogitoxigenin to go to a dianhydro derivative is so strong that special procedures are necessary for the formation of monoanhydro derivatives. Two isomeric anhydro derivatives of dihydrogitoxigenin corresponding to the two dihydrogitoxigenins have been prepared (63) by subjecting the appropriate dihydrogitoxigenin to the action of zinc chloride in acetic anhydride. In this way, monoanhydrodiacetates were obtained, wherein the tertiary hydroxyl group was removed and the other two hydroxyl groups were acetylated. The double bond in both derivatives resists catalytic hydrogenation.

Periplogenin easily forms a trianhydro derivative by loss of its three hydroxyl groups under the influence of acid (52). In this substance all of the double bonds can be catalytically reduced, thus indicating that they are not in a benzenoid arrangement as in trianhydrostrophanthidin. Absorption spectra data substantiated this conclusion (25).

Other anhydro derivatives of various genins have already been discussed in connection with other phases of the work, such as anhydroisostrophanthonic dimethyl ester and the anhydro derivatives of ouabagenin and uzarigenin.

### *J. Steric considerations and rearrangements*

While the degradation of digitoxigenin to etiocholic acid at first glance might seem to indicate that the aglycones belong to the cholic acid series, such a conclusion is not warranted. During the series of reactions leading to etiocholic acid the hydroxyl group in digitoxigenin on carbon atom 14 was removed and the resulting double bond then hydrogenated. Undoubtedly, this hydrogenation reestablished asymmetry on this carbon

atom, hence any conclusion of the original configuration of the aglycone at this point is extremely uncertain. At the same time, as has been mentioned, deductions from the degradation of dianhydrouzarigenin to etioallocholanolic acid are uncertain for similar reasons.

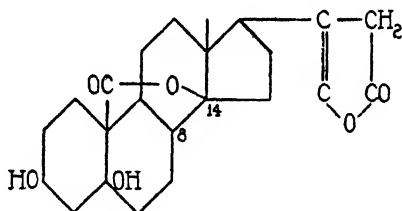
It is possible, however, to make certain limited deductions regarding the manner of linkage of the rings in some of the aglycone derivatives. In digitoxigenin, and therefore in gitoxigenin, rings I and II are probably linked in a *cis* configuration as in the cholanolic acid series, for there is no apparent reason for expecting disruption of the asymmetry on carbon atom 5 on the way to etiocholanolic acid. However, in the case of strophanthidin and periplogenin such a statement is rendered uncertain, since asymmetry on this carbon atom was destroyed and then reestablished in the correlation of these aglycones with digitoxigenin. There is no evidence beyond this for placing the aglycones definitely in either the cholanolic or allocholanolic acid series.

Certain reactions of strophanthidin and its derivatives involve rearrangements which must affect the centers of asymmetry of the molecule. The aldehyde group of normal or  $\alpha$ -isostrophanthidin or  $\alpha$ -isostrophanthidic acid exhibits no tendency to exist in the form of a lactal with  $\text{OH}^{\text{III}}$ . Similarly,  $\alpha$ -isostrophanthic acid, in which the aldehyde group has been oxidized to carboxyl, shows no tendency to lactonize on this hydroxyl group. However, if  $\alpha$ -isostrophanthidic acid be boiled with alkali, an isomerization occurs, and the isomerized acid,  $\beta$ -isostrophanthidic acid, can be isolated through its sparingly soluble ammonium salt (71). The aldehyde group of this substance exists either as a lactal involving  $\text{OH}^{\text{III}}$ , as shown by its oxidation with hypobromite to  $\beta$ -isostrophanthic lactone acid (LVIII), or as the free aldehyde, as shown by its oxidation with permanganate to  $\beta$ -isostrophanthic acid which readily lactonizes, in contrast to the  $\alpha$ -isomer. This change is not undergone by  $\alpha$ -isostrophanthic acid, where the aldehyde group has been oxidized to carboxyl, a fact which at first led to its explanation on the usual basis of a change of the aldehyde group from a position *trans* to  $\text{OH}^{\text{III}}$  to a *cis* position by enolization on an adjacent CH group under the influence of alkali.

However, the placing of the aldehyde group on a quaternary carbon atom, 10, necessitated a different explanation. The most logical one appears to be based on the assumption that in the  $\alpha$  series, rings I and II are linked in a *trans* arrangement as in allocholanolic acid. Under the influence of alkali a rearrangement at carbon atom 5 occurs, so that in the  $\beta$  series the two rings are *cis* to each other as in cholanolic acid, an arrangement which permits interaction of the aldehyde or carboxyl group on carbon atom 10 with  $\text{OH}^{\text{III}}$  (78a). Such an explanation is supported by a study of the atomic model and by the persistence of the differences between the

two series through the  $\alpha$ - and  $\beta$ -isostrophanthonic esters. However, both isostrophanthonic esters yield the same anhydroisostrophanthonic esters, owing to loss of asymmetry on carbon atom 5 (79). Whether during the reduction of  $\alpha$ -isostrophanthidic acid to isoperiplogenenic acid by the method of Kishner and Wolff a similar rearrangement occurs under the influence of the sodium ethylate remains to be determined.

Another type of isomerization noted in certain derivatives appears to involve the centers of asymmetry located on carbon atoms 8 and 14. When strophanthidin is dissolved in strong acid, pseudostrophanthidin is formed, which has been shown to contain a lactal group between the aldehyde group and  $\text{OH}^I$ . Similarly, from strophanthidinic acid a dilactone, strophanthidinic lactone, results (LX) (57). A *trans* configuration between rings II and III, as assumed in many sterols, would prevent the formation of an oxidic bridge between the aldehyde group and  $\text{OH}^I$  in strophanthidin. After isomerization to pseudostrophanthidin, rings II and III may be in a *cis* configuration, an arrangement which a study of the



LX

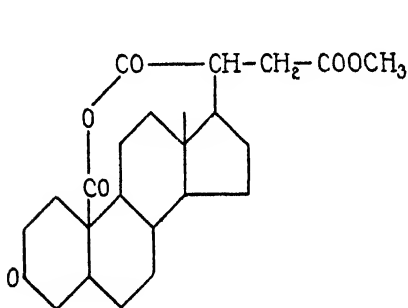
model shows to permit formation of such a bridge readily. Another explanation for this isomerization may be postulated on a preliminary removal of  $\text{OH}^I$  with the formation of a double bond between carbon atoms 8 and 14, followed by subsequent addition to this double bond with the formation of an oxidic linkage on carbon atom 8.

When  $\beta$ -isostrophanthic acid is dissolved in strong hydrochloric acid, in addition to lactonization of the carboxyl group on carbon atom 10 with  $\text{OH}^{III}$  a further isomerization occurs (71). The substance differs from  $\beta$ -isostrophanthic lactone acid in its physical properties. It has been called  $\delta$ -isostrophanthic lactone acid. Similarly,  $\alpha$ -isostrophanthic acid under the same conditions is isomerized to  $\gamma$ -isostrophanthic acid, except that in this case no lactone formation occurs. The same center of asymmetry is involved in both cases. Whether this type of isomerization is the same as that which occurs in the case of the formation of pseudostrophanthidin remains a subject for future investigation. A similar type of isomerization has also been noticed in the case of digitoxigenin derivatives (77).

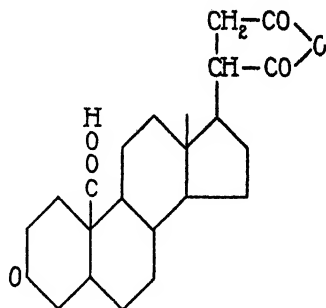
Finally, a derivative of strophanthidin which owes its origin to a change

in the centers of asymmetry of the molecule is the anhydride ester (LXI) (60). By the use of reactions already discussed,  $\text{OH}^{\text{I}}$  and  $\text{OH}^{\text{II}}$  were removed and the double bonds hydrogenated to give the keto acid anhydride (LXII). This on treatment with methyl alcoholic hydrogen chloride gave the anhydride (LXI), the formation of which appears to involve a rather long stretch. However, from a study of the model, it is apparent that this anhydride formation is quite possible, if during the hydrogenation of the double bond arising from loss of  $\text{OH}^{\text{I}}$  asymmetry is reestablished on carbon atom 8 in such a manner that the original *trans* configuration of rings II and III becomes *cis*.

The oxidation product of gitoxigenin,  $\alpha$ -oxoisodigitoxigenone, undergoes isomerization to a  $\beta$ -compound in acid or alkaline solution (78). This appears to be readily explained on the basis of the well-known epimeriza-



LXI



LXII

tion of a CH group (carbon atom 17) adjacent to a carbonyl group (carbon atom 16).

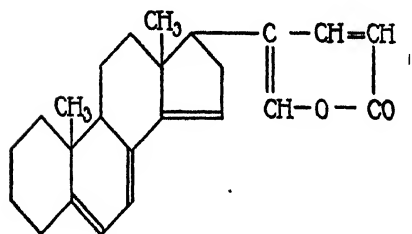
### K. The squill aglycones

Stoll and coworkers have made some progress on the problem presented by scillaridin A. This aglycone, in contrast to the aglycones previously discussed, does not give the Legal test. However, the presence of a lactone group has been clearly demonstrated, which, however, apparently is not a  $\Delta^{8,9}$ -lactone of the type common to the previously considered aglycones. Stoll, Hoffmann, and Helfenstein (156) by the action of methyl alcoholic potassium hydroxide have succeeded in opening the lactone group and at the same time esterifying the carboxyl group liberated to give scillaridinic methyl ester. The hydroxyl group liberated then readily loses water with a second hydroxyl group in reactive proximity with the formation of an oxidic bridge to give isoscillaridinic-A-acid methyl ester. (The term "iso" is used in this connection only to denote the presence of an oxidic ring,

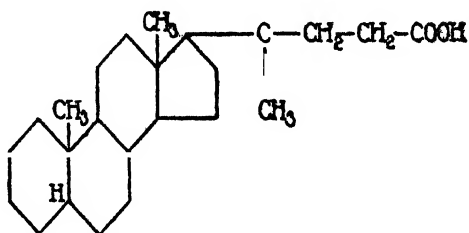
and is not synonymous with the term as used in connection with the isomerization of the other aglycones.) However, by rapid manipulation it was possible to methylate the hydroxyl group originally bound in lactone formation, with the formation of methyl scillaridinic-A-methyl ester. This, together with the formation of alkali salts, was taken to indicate the phenolic nature of the lactone hydroxyl group in scillaridin A.

Scillaridin A loses another molecule of water on treatment with acid. This anhydroscillaridin A on treatment with alkali no longer gives an iso compound, showing that the hydroxyl group of scillaridin A which functions in the formation of the oxidic bridge during the isomerization is no longer present.

The hydrogenation of scillaridin A, anhydroscillaridin A, and their derivatives has been described (157 b) and leads to the conclusion that the former contains four double bonds and the latter five. Scillaren A con-



LXIII



LXIV

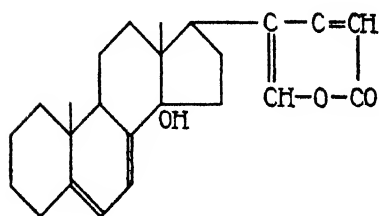
Allocholanic acid

tains but three double bonds, one hydroxyl group being removed from the aglycone during hydrolysis. In all cases, partial reduction of the lactone occurred, giving a mixture of the saturated lactone and deoxyacid.

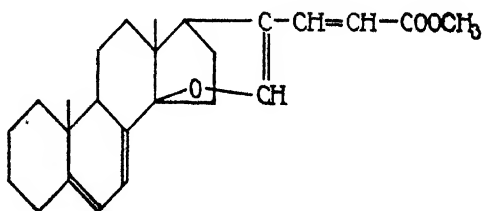
From the mixture of isomers obtained by complete reduction of anhydroscillaridin A to the saturated acid, scillanic acid, one component has very recently been obtained pure by Stoll, Hoffmann, and Helfenstein (155). On further examination this acid was found to be identical with allocholanic acid (LXIV). This finding furnished confirmation of the suspected close relationship between scillaridin A and the bile acids. In addition, however, it forced a revision of the previously adopted formulations for scillaridin A and therefore for scillaren A and proscillaridin A. Stoll and coworkers had previously accepted  $C_{26}H_{32}O_3$  as representing scillaridin A. Inasmuch as the formulation for allocholanic acid has been definitely established to be  $C_{24}H_{40}O_2$ , it follows that scillaridin A must be revised to  $C_{24}H_{30}O_3$ .

In the light of these latest findings, the structure of anhydroscillaridin A is represented by Stoll, Hoffmann, and Helfenstein by formula LXIII;

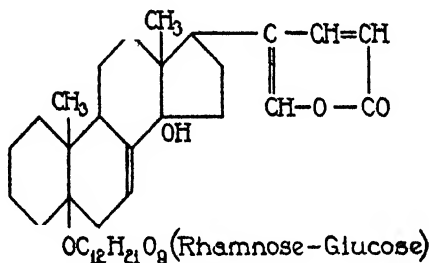
on hydrogenation this yields allocholanolic acid (LXIV). Scillaridin A is represented by formula LXV. From this it is obvious that the previously advanced idea that the hydroxyl group of the lactone group is of phenolic character must be revised, since the hydroxyl group in question unquestionably is located on one of the carbon atoms of the side chain. The presence of the unsaturated  $\delta$ -lactone in contrast to the  $\gamma$ -lactones of the members of the digitalis-strophanthin group accounts for the failure of scillaridin A to give the Legal test and also for the reduction to the saturated deoxyacid.



LXV  
Scillaridin A



LXVI



LXVII  
Scillaren A

The remaining hydroxyl group of scillaridin A is placed on carbon atom 14, in order to bring it into reactive proximity to the lactone hydroxyl group of the side chain to account for the formation of isoscillaridinic-A-acid methyl ester (LXVI). The evidence for the positions assigned to the double bonds rests on a less secure basis,—namely, certain analogies to ergosterol exhibited by scillaridin A, in particular the Rosenheim trichloro-acetic acid color test.

Finally, a complete formula (LXVII) for scillaren A has been advanced. The evidence for placing the hydroxyl group which bears the sugar residue on carbon atom 5 consists in the resistance to hydrolytic cleavage exhibited by the glycoside. From this it is argued that the hydroxyl group in ques-

tion is probably tertiary. However, whether the difficulty of hydrolysis of the glycosidic linkage is due to this factor or whether it may be conditioned by the presence of the normal deoxyhexose, rhamnose, as in the case of the hydrolysis of ouabain, remains to be determined.

Nothing is known concerning scillaridin B.

#### IV. NITROGENOUS CARDIAC PRINCIPLES

##### A. *The toad poisons*

Any account of the digitaloid substances would be incomplete without mention of another group of very interesting compounds which are, however, of animal origin—the so-called toad venoms. These substances, which exhibit a potent digitalis action, are secreted by certain (parotid) glands on the surface of the animals. Abel and Macht (1) were the first to report the isolation of a non-nitrogenous, crystalline principle, bufagin, from such a secretion of the tropical toad, *Bufo aqua (marinus)*. In addition, a relatively large amount of adrenalin was isolated.

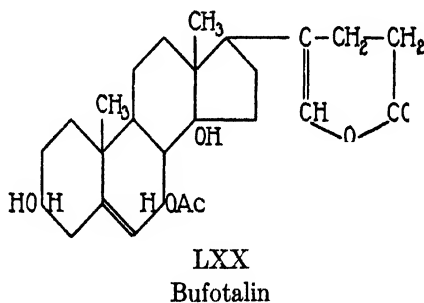
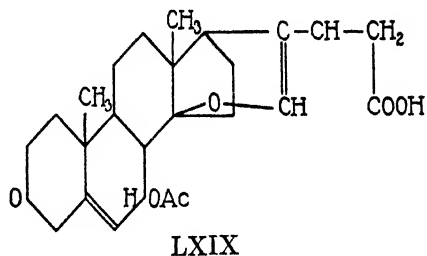
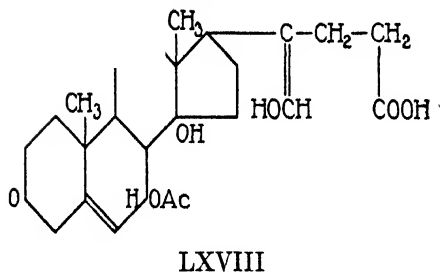
The chemistry of these materials has recently been developed to a considerable extent. As in the case of the plant glycosides, confusion has been occasioned by uncertainty as to the source of the material under examination. This has particularly been the case in the study of Ch'an Su or Senso, the dried venom of the Chinese toad, where conflicting reports have come from several workers.

Wieland and coworkers have made an extensive study of the principle from *Bufo vulgaris*. A substance, bufotalin (186),  $C_{26}H_{36}O_6$ , was first obtained which corresponded to, but was not identical with, bufagin. Subsequently, Wieland and Alles (180) obtained a non-glycosidal, neutral, nitrogenous substance, bufotoxin,  $C_{40}H_{62}O_{11}N_4$ , which was shown to be a conjugation of bufotalin with arginine and suberic acid. Thus it was concluded that bufotalin is a sort of "genin" of the toad poison in question, bufotoxin, in which the suberylarginine parallels somewhat the position of the sugar in the non-nitrogenous glycosides. On hydrolysis it was shown that bufotoxin, which contains one double bond, yields not bufotalin but a still more unsaturated substance, bufotalein,  $C_{24}H_{30}O_3$ , along with suberylarginine and acetic acid.

Oxidation of bufotalin with chromic acid leads to a monoketone, bufotalone; hence it contains one secondary hydroxyl group. Two more of the oxygens are contained in an acetoxyl group which can be removed on saponification. A lactone accounts for two more oxygens and the sixth is in the form of a tertiary hydroxyl group. Bufotalin, therefore, is the acetate of a doubly unsaturated trihydroxylactone,  $C_{24}H_{34}O_5$ . However, since the toad poisons, as far as they have been investigated, do not give the Legal nitroprusside reaction, it must be concluded that neither of the double

bonds of bufotalin is in the lactone ring, or else that the lactone is not a  $\gamma$  but rather a  $\delta$  one.

Concentrated hydrochloric acid removes the acetoxyl and tertiary hydroxyl groups from bufotalin to give bufotalein. After acetylation of the remaining hydroxyl group, catalytic hydrogenation of acetylbufotalein leads to a mixture of acetylbufotalans, the fully saturated acetoxylactone, and the acetate of a monobasic acid arising from reduction of the lactone (183). After removal of the acetyl group of this acid, the remaining hydroxyl group can be replaced by hydrogen by distillation *in vacuo* and catalytic hydrogenation of the resulting unsaturated acid. The final



product is isobufocholanic acid,  $C_{24}H_{40}O_2$ , which, however, is not identical but isomeric with any of the known cholanic acids. The isomerization may be due to the formation of isomerides on hydrogenation.

Very recently, Wieland and Hesse (182) have reported the dehydrogenation of bufotalin with selenium. They obtained a hydrocarbon believed to be chrysene, which has also been obtained from the sterols. In addition, they have succeeded in opening the lactone ring of bufotalone. The free acid obtained, however, was still missing a water molecule. It was concluded that the enolized aldehyde group had participated in the formation of a new oxidic linkage with one of the remaining hydroxyl groups. This transformation is represented by formulas LXVIII and LXIX, from which Wieland's tentative structure for bufotalin is at once obvious (LXX).

The venom of the Japanese toad, *Bufo japonicus* (or *Bufo vulgaris* for-



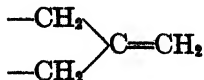
*mosus*), has been studied by Kotake (115) and Wieland and Vocke (185). The former isolated a substance, gamabufotalin (gamma being the Japanese word for toad), to which he gave the formula  $C_{27}H_{38}O_6$ . This substance, on saponification, in addition to opening the lactone was reported to lose  $C_3H_5O$  to give a non-lactonizing gamabufotalinic acid. On catalytic hydrogenation, gamabufotalin loses  $C_3H_5O$  and absorbs six atoms of hydrogen to give a substance of the formula  $C_{24}H_{38}O_5 \cdot C_2H_5OH$ . In addition, gamabufotalin contains two acylatable hydroxyl groups.

The observations of Wieland and Vocke are somewhat at variance with Kotake's. They isolated gamabufotoxin,  $C_{38}H_{60}O_{10}N_4$ , which contains a lactone and one double bond. It is a suberylarginine derivative, but the "genin" is different from the bufotalin isolated from *B. vulgaris*. Direct hydrolysis of gamabufotoxin leads to the formation of an anhydrogamabufagenin,  $C_{24}H_{32}O_4$ . In addition to gamabufotoxin, gamabufogenin,  $C_{24}H_{34}O_6$ , was isolated in small amounts as such. On treatment with concentrated hydrochloric acid gamabufagenin loses one molecule of water to give an anhydrogamabufagenin, which is not identical with that obtained by direct hydrolysis of gamabufotoxin. However, the latter can be isomerized to the former by the action of strong acid. In their behavior towards acid these two substances differ from bufotalin, which loses one acetyl group and one molecule of water under the influence of acid. Gamabufagenin is a doubly unsaturated trioxylactone in which two of the hydroxyl groups are acylatable and hence presumably secondary. Since its anhydro derivative still absorbs only two molecules of hydrogen, the new double bond in the latter is inert. Gamabufogenin is very similar to, but not identical with, Kotake's gamabufotalin. However, the hydrogenation products of the two seem to be identical. This may be taken to indicate that Kotake's material is an acetyl derivative of a  $C_{24}$  genin, in which case his  $C_3H_5O$ , which is lost, would become  $C_2H_2O$ .

More recently, Chen, Jensen, and Chen (14) have reported the isolation of a gamabufagin from identified *B. formosus*, presumably the same species investigated by the earlier workers, which gave analytical figures corresponding to Kotake's gamabufotalin. The gamabufotoxin obtained by them, however, more closely resembled Wieland's material.

Jensen and Chen (90) have examined the bufagin of Abel and Macht. They succeeded in isolating from the secretion of *B. marinus* a crystalline bufotoxin, marinobufotoxin, for which the formula  $C_{42}H_{64}O_{11}N_4$  was given. At the same time the formula for bufagin was revised to  $C_{28}H_{36}O_6$  and a monoacetyl derivative of the substance was noted. Subsequently, Jensen (91) noted the formation of formic acid from bufagin under the action of alkali and considered it to be a formoyl derivative of a triply unsaturated (hydrogenation), monohydroxy,  $C_{23}$  lactone, thereby bringing it into con-

formity with the plant aglycones. A still further revision of the formula for marinobufotoxin by Jensen and Evans (92) to  $C_{38}H_{55}O_{10}N_4$  has been made more recently. Observations were also made which indicated that the formic acid produced by alkali does not have its origin in a formoyl group in the bufagin, but rather in a



grouping which breaks at the double bond to give formaldehyde. The latter then undergoes a Cannizzaro reaction with the production of formic acid.

The bufagins and bufotoxins of a number of other species of toads have been isolated by Chen and Chen (16). Inasmuch as the active principles gave the impression of being different substances, these workers have proposed using the name of the species from which the substances are obtained as a prefix. Bufagin and bufotoxin thus become generic terms.

The Chinese have long made use of a remedy known as Ch'an Su (in Japan, Senso) which purports to consist of the dried venom of a Chinese toad. Chen and Chen (15) are of the opinion that *Bufo bufo gargarizans* is the source of Ch'an Su. However, owing to the conflicting results obtained by various investigators, this surmise would seem to be open to question. Shimizu (152), who was the first to attempt its investigation, isolated a crystalline substance from Senso, either identical or isomeric with Wieland's bufagin, as well as an amorphous bufotoxin. Subsequently, Kodama (111) isolated a bufagin and gave it the formula  $C_{27}H_{34}O_7$ . He also obtained an amorphous bufotoxin.

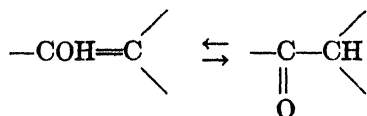
Kotake (116), the first to attempt an exhaustive study of the chemistry of the constituents of Senso, isolated a cinobufagin (here prefixed by "cino-" in line with Chen's suggestion for nomenclature) to which he assigned the formula  $C_{29}H_{38}O_7$ . It contains an acetyl group which is removed by alkaline saponification, which simultaneously opens the lactone. Cinobufagin gives a diacetate,  $C_{33}H_{42}O_9$ , but on oxidation with chromic acid only a monoketone is formed. On catalytic hydrogenation two isomeric tetrahydrocinobufagins,  $C_{29}H_{42}O_7$ , are formed. Kotake's cinobufagin therefore contains a lactone, an acetoxyl group, one secondary hydroxyl group, and two double bonds, leaving one oxygen atom to be accounted for. From the mother liquors from the cinobufagin, after treatment with hydrogen chloride gas, he was able to isolate a chloro derivative, apparently corresponding to Kodama's bufotoxin (111), to which the formula  $C_{27}H_{38}O_6Cl$  was assigned. It is considered to be derived

from cinobufagin by loss of the acetoxyl group and replacement of one hydroxyl group by chlorine.

Jensen and Chen (89) have reported the isolation from Ch'an Su of a cinobufotoxin,  $C_{43}H_{64}O_{12}N_4$ , and a cinobufagin,  $C_{25}H_{38}O_7$ , agreeing with Kotake's substance. The former, as expected, was found to be a conjugation of a genin, which was not isolated, with suberylarginine. Subsequently, Jensen (91, 92) revised these formulas to  $C_{32}H_{58}O_{11}N_4$  and  $C_{25}H_{32}O_6$ , respectively. The usual methods accounted for all the oxygens as a lactone, an acetoxyl group, one secondary hydroxyl group, and one tertiary hydroxyl group. Cinobufagin therefore appears to be an acetyl derivative of a  $C_{23}$  genin.

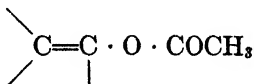
Kondo and Ikawa in a series of studies have elucidated the chemistry of a bufotalin isolated from Senso which, although first giving the impression of being identical with Wieland's substance, appeared on later study to be quite different from the ones previously reported (112). This they have called pseudobufotalin. From the Senso with which they worked, they failed to isolate bufotoxin and concluded that perhaps it may have been decomposed during drying of the toad venoms.  $\psi$ -Bufotalin possesses the formula  $C_{26}H_{36}O_6$  and is an acetyl derivative of a substance  $C_{24}H_{34}O_5$ ,—deacetyl- $\psi$ -bufotalin.  $\psi$ -Bufotalin contains one acylatable hydroxyl group, but differs from Wieland's bufotalin in the behavior of the deacetyl compound. Once the original acetyl group is removed, deacetyl- $\psi$ -bufotalin gives only a monoacetate, the hydroxyl group originally acetylated being resistant to reacetylation. Contrasting with bufotalin,  $\psi$ -bufotalin when treated with strong acid retains the acetyl group, giving only a mono-anhydro- $\psi$ -bufotalin, compared with bufotalin from bufotalin.  $\psi$ -Bufotalin is also different from Kotake's bufagin.

$\psi$ -Bufotalin on oxidation with chromic acid gives a monoketone,  $\psi$ -bufotalone, which in turn gives a monoöxime (113). This on saponification loses the acetyl group, and simultaneously the lactone is opened to give deacetylbufotalonic acid,  $C_{24}H_{34}O_6$ . From the methyl ester of the latter compound a monoacetate was obtained, indicating that the hydroxyl group originally bound in lactone formation is primary or secondary. But deacetyl- $\psi$ -bufotalonic ester gives a dioxime. This is explained by a keto-enol tautomerism involving one of the hydroxyl groups, and indicates that the arrangement



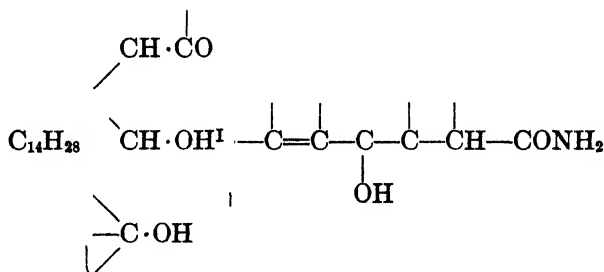
is present. That the hydroxyl group involved in this change is the one originally acetylated in  $\psi$ -bufotalin is shown by the production of a mono-

oxime from deacetyl- $\psi$ -bufotalin itself. This interpretation is strengthened by the observation that  $\psi$ -bufotalin on catalytic hydrogenation absorbs two molecules of hydrogen to give two isomeric tetrahydro- $\psi$ -bufotalins, which on saponification give deacetyltetrahydro- $\psi$ -bufotalins. However, in these substances the originally acylated hydroxyl group has become active, since diacetates were obtained. The retention of the tertiary hydroxyl group was indicated by the formation of a monochloro compound. Thus, the group

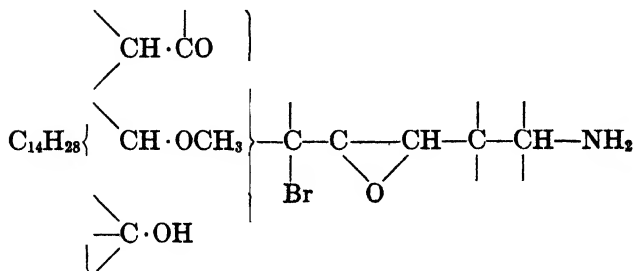


is present in  $\psi$ -bufotalin.

In a third paper the same workers have placed the second double bond of  $\psi$ -bufotalin (114). Deacetyl- $\psi$ -bufotalin on treatment with ammonia yields an amide (LXXI) by opening of the lactone. Bromine and sodium



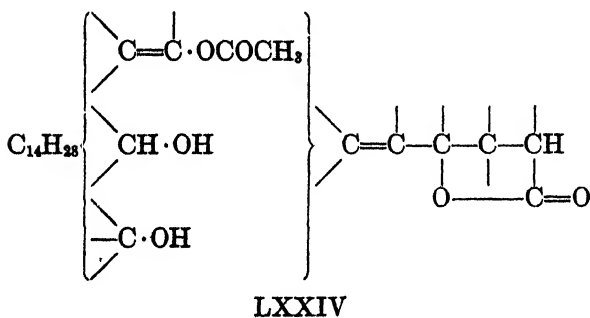
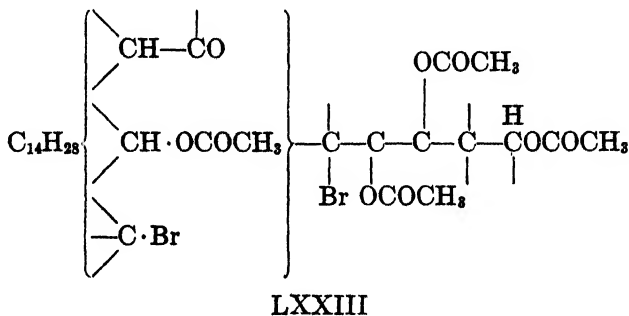
LXXI



LXXII

methylate yielded the urethan, with simultaneous methylation of the secondary hydroxyl group. At the same time, hypobromous acid added to the double bond with the formation of a bromohydrin from which water was spontaneously lost, resulting in the formation of an ethylene oxide. Hydrolysis with alcoholic alkali gave the methoxyamine (LXXII),

which was demethylated by heating with hydrogen bromide in acetic acid. The tertiary hydroxyl group was retained, as shown by conversion to a dibromide. Finally, acetic anhydride opened the ethylene oxide to yield a dibromotetraacetate (LXXIII). Thus, the second double bond in  $\psi$ -bufotalin was shown to be  $\alpha, \beta$  to the lactone, and  $\psi$ -bufotalin may be represented by formula LXXIV.



### B. *Erythrophloeum guineense*

The bark of this tree, often called "sassy-bark," has long been the source of an ordeal poison of the natives of East Africa. A graphic description of its use is given by Proctor (146). The active principle of the bark, while displaying a powerful digitalis action, contains nitrogen and falls in the alkaloid class. Gallois and Hardy (34) first investigated it and reported the isolation of a crystalline alkaloid, to which they gave the name "erythrophleine" and which gave a crystalline hydrochloride and platini-chloride. Subsequently Harnack and Zabrocki (38) took up its study, but obtained erythrophlein only as an unstable oil. On boiling with acid or alkali it is decomposed, yielding a partly crystalline, nitrogen-free erythrophleic acid. They surmised that erythrophlein probably consisted of a nitrogenous side chain joined to a nitrogen-free complex to which the physiological action is due. In a later paper Harnack (39) succeeded in

obtaining solid platinichloride and potassium bismuth iodide salts from analyses of which he deduced formulas of either  $C_{23}H_{43}NO_7$  or  $C_{25}H_{45}NO_7$  for erythrophlein. Its decomposition with acid gave methylamine and erythrophleic acid,  $C_{27}H_{38}O_7$  or  $C_{27}H_{40}O_7$ . More recently, Power and Salway (144) obtained erythrophlein as an oil and checked Harnack's formulation. Maplethorpe also failed to obtain it crystalline (127). Petrie (140) reported *Erythrophloeum laboacherii*, a native of Australia, to yield the same erythrophlein as that previously obtained. Kamerman (93) reported the same substance from *E. lasianthum*, and developed a method for isolating it as the phosphotungstate.

#### V. THE SUGAR COMPONENTS OF THE CARDIAC GLYCOSIDES

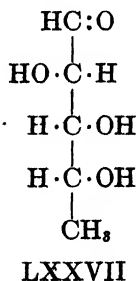
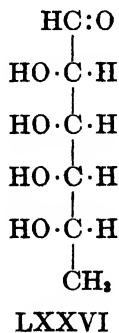
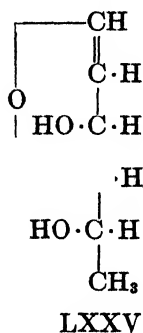
In the preceding discussion mention has been made of the sugars which have been isolated after hydrolysis of the cardiac glycosides. Inasmuch as some of them have been shown to possess unusual structural features, it will be profitable to treat them in more detail. Digitoxose, cymarose, and sarmentose are 2-deoxysugars, and with the exception of deoxyribose from thymus nucleic acid (122) are the only members of this group of sugars which have been encountered in nature. They are characterized by their lability towards acid as compared with the usual hexoses, and by the ease with which their glycosides undergo hydrolysis. The Keller-Kiliani test (the production of a blue color when an acetic acid solution of the sugar containing iron is allowed to come in contact with a layer of sulfuric acid) is characteristic of the group.

##### A. Digitoxose

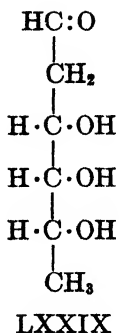
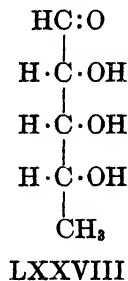
This sugar was first isolated by Kiliani (102) from digitoxin. He assigned to it the formula  $C_6H_{12}O_4$ , noted that in its reaction with phenylhydrazine only a phenylhydrazone rather than an osazone was formed (103), and obtained acetic acid upon oxidation of it with silver oxide (104). Later he showed it to be an aldose by the formation of digitoxonic acid upon oxidation with bromine water, and obtained  $\alpha,\beta$ -dihydroxyglutaric acid and mesotartaric acid on oxidation with nitric acid (105). These facts were sufficient for the derivation of the structure  $CH_2 \cdot (CHOH)_3 \cdot CH_2 \cdot CHO$  or that of a 2-deoxyhexomethyllose. In a later paper, Kiliani (106) concluded that the hydroxyl groups on  $C_3$  and  $C_4$  are *cis* to one another. This was supported by the application of Hudson's rule to digitoxonic lactone and to the lactone of digitoxoseheptonic acid derived from the sugar by the cyanohydrin reaction. In addition, these hydroxyl groups were assigned positions to the left of the chain.

Windaus and Schwarte (195), starting with a substance obtained by Cloetta (17) by vacuum sublimation of digitoxin, indicated that the hy-

droxyl group on C<sub>5</sub> was also *cis* to those on C<sub>3</sub> and C<sub>4</sub>. Cloetta's substance was shown to be an anhydro derivative of digitoxose of the glucal type, to which the formula LXXV was assigned. By oxidation of this glucal with perbenzoic acid, an aldohexamethylose was obtained to which was assigned



or



the configuration LXXVI, on the basis of physical constants and the properties of the phenylosazone, taken together with Kiliani's work.

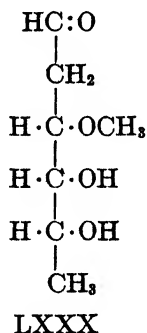
Micheel (130), however, has shown that Hudson's rule apparently does not hold in this case. The above glucal (LXXV) on ozonization leads to a pentomethylose (LXXVII or LXXVIII). This was shown to possess the

same configuration on C<sub>4</sub> and C<sub>5</sub> of the digitoxose chain as *d*-arabomethyl-ose, by the preparation of identical phenyl- and *p*-bromophenyl-osazones from both sources. Hence, since the hydroxyl groups on C<sub>3</sub> and C<sub>4</sub> are *cis* to one another, it follows that all three hydroxyl groups are *cis* and that digitoxose belongs to the *d*-series. Digitoxose therefore is represented by formula LXXIX and is 2-deoxyallomethyl-ose.

### B. Cymarose

Cymarose was first obtained by Windaus and Hermanns (193) from cymarin. They showed it to be a methyl ether of a 2-deoxyhexomethyl-ose and suggested that it might be a methyl ether of digitoxose. Recently Elderfield has shown the position occupied by the methoxyl group to be C<sub>3</sub>, and has demonstrated the configurational identity with digitoxose. When oxidized with 50 per cent nitric acid, cymarose yielded the lactone of  $\alpha$ -hydroxy- $\beta$ -methoxyglutaric acid (27), thus rendering probable the allocation of the methoxyl group on C<sub>3</sub>. This was substantiated by the preparation of two different fully methylated lactones from cymarose, one of which possesses a  $\gamma$ -lactone ring and the other a  $\delta$ -lactone ring. Thus, both of the hydroxyl groups on C<sub>4</sub> and C<sub>5</sub> are unsubstituted.

The relationship of cymarose to digitoxose was shown by the preparation of identical fully methylated  $\gamma$ -lactones from both sugars (27). Cymarose therefore is represented by formula LXXX.



### C. Sarmentose

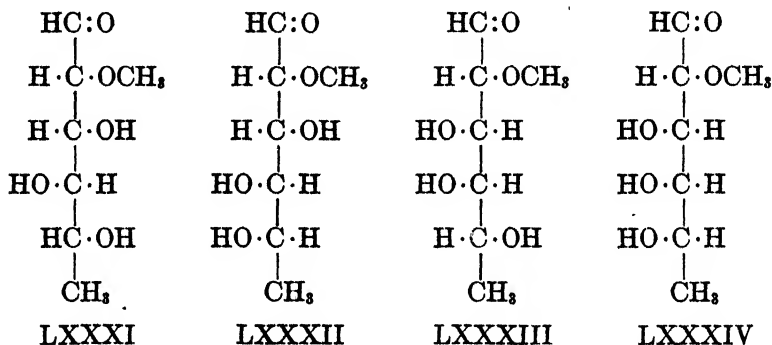
This sugar was isolated from sarmentocymarin by Jacobs and Bigelow (49). It is a methyl ether of a 2-deoxyhexomethyl-ose isomeric with cymarose. The position occupied by the methoxyl group and the configuration are unknown at present.

### D. Digitalose

Digitalose differs from the above sugars in that it is not a 2-deoxysugar. However, it does contain a methoxyl group. It was obtained as a syrup by



Kilian (107) from digitalinum verum. On oxidation with bromine water, crystalline digitalonic lactone was obtained, which was shown to have the formula  $C_7H_{12}O_5$ . From this he concluded that digitalose was  $C_7H_{14}O_5$ . He also obtained acetic acid by oxidation of the lactone with silver oxide, thus indicating the presence of a terminal methyl group. Further, digitalonic lactone gave on oxidation with nitric acid an  $\alpha,\beta$ -dihydroxy- $\alpha'$ -methoxyglutaric acid (108). Schmidt and Zeiser (149) have recently shown that this oxidation product after complete methylation is identical with *l*-arabotrimethoxyglutaric acid. From this it follows that digitalose is represented by one of the formulas LXXXI to LXXXIV.



#### *E. Linkage of the sugars with the aglycones*

Jacobs and Hoffmann (84) have shown that in cymarín the sugar is presumably joined in glycosidic union with the secondary hydroxyl group ( $OH^{III}$ ) of strophanthidin. Cymarín on acetylation with acetic anhydride in pyridine solution yields a monoacetyl derivative. If it be accepted that acetylation has occurred on the free hydroxyl group of the cymarose unit, then the strophanthidin has remained unacetylated. Since strophanthidin itself under such conditions forms only a monoacetyl derivative, the conclusion appears warranted that the ordinarily acetyltable  $OH^{III}$  is the point of glycosidic union. While no direct evidence is at hand regarding this point in respect to the other glycosides, they probably will be found to contain a similar glycosidic linkage.

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## VI. REFERENCES

- (1) ABEL, J. J., AND MACHT, D. I.: *J. Pharm.* **3**, 319 (1911-12).
- (2) ARNAUD: *Compt. rend.* **106**, 1011 (1888); **107**, 1162 (1888); **126**, 346, 1208, 1654 (1898).
- (3) ARNAUD: *Compt. rend.* **107**, 179 (1888).
- (4) ARNAUD: *Compt. rend.* **108**, 1255 (1889); **109**, 701 (1889).
- (5) ARNAUD: *Compt. rend.* **109**, 701 (1889).
- (6) AYYAR, P. R.: *Proc. Indian Sci. Congr.* **15**, 161 (1928).
- (7) BLAS, M. C.: *Bull. acad. roy. méd. Belg.* **2**, 745 (1868).
- (8) BOEHM, R.: *Arch. exptl. Path. Pharmacol.* **26**, 165 (1890).
- (9) BOWRY, J. J.: *J. Chem. Soc.* **33**, 252 (1878).
- (10) BRAUNS, D. H., AND CLOSSON, O. E.: *J. Am. Pharm. Assoc.* **2**, 489, 604, 715 (1913).
- (11) BRIEGER, L.: *Berlin. klin. Wochschr.* **39**, 277 (1902); *Deut. med. Wochschr.* **34**, 45 (1899); **35**, 637 (1900).
- (12) CERVELLO, V.: *Arch. exptl. Path. Pharmacol.* **15**, 235 (1882).
- (13) CHEN, K. K., AND CHEN, A. L.: *J. Pharm.* **49**, 561 (1933); *J. Biol. Chem.* **105**, 231 (1934).
- (14) CHEN, K. K., JENSEN, H., AND CHEN, A. L.: *J. Pharm.* **49**, 26 (1933).
- (15) CHEN, K. K., AND CHEN, A. L.: *J. Pharm.* **49**, 543 (1933).
- (16) CHEN, K. K., AND CHEN, A. L.: *J. Pharm.* **47**, 281 (1933); **49**, 526, 561 (1933); *Arch. intern. pharmacodynamie* **47**, 297 (1934).
- (17) CLOETTA, M.: *Arch. exptl. Path. Pharmacol.* **88**, 113 (1920).
- (18) CLOETTA, M.: *Arch. exptl. Path. Pharmacol.* **112**, 261 (1926).
- (19) CUSHNY, A.: *Digitalis and its Allies*. Longmans, Green and Co., London (1925).
- (20) DELATTRE, A.: *J. pharm. chim.* [7] **6**, 292 (1912).
- (21) DEVRY, J. E.: *Sitzb. Akad. Wiss. Wien.*, January, 1864.
- (22) DEVRY, J. E., AND LUDWIG, E.: *J. prakt. Chem.* **103**, 253 (1868).
- (23) DEVRY, J. E.: *Pharm. J.* **12**, 457 (1881).
- (24) D. R. P. 255,537.
- (25) ELDERFIELD, R. C., AND ROTHEN, A.: *J. Biol. Chem.* **106**, 71 (1934).
- (26) ELDERFIELD, R. C., AND JACOBS, W. A.: *J. Biol. Chem.* **107**, 143 (1934); *Science* **79**, 279 (1934).
- (27) ELDERFIELD, R. C.: *Science* **81**, 440 (1935); *In press*.
- (28) FAUST, E. S.: *Arch. exptl. Path. Pharmacol.* **48**, 272 (1902).
- (29) FEIST, F.: *Ber.* **31**, 534 (1898); **33**, 2063, 2069, 2091 (1900).
- (30) FRASER, T. R.: *Strophanthus hispidus; its Natural History, Chemistry, and Pharmacology*. Neill and Co., Edinburgh, 1891.  
FRASER, T. R., AND DOBBIN, L.: *Trans. Roy. Soc. Edinburgh* **37**, 1 (1891-3).
- (31) FRASER, T. R., AND TILLIE, J.: *Arch. intern. pharmacodynamie* **5**, 349 (1892).
- (32) FROMHERZ, K.: *Munch. med. Wochschr.* **75**, 818 (1928).
- (33) FUECKELMANN, J. M.: *Sitzber. Abhandl. naturforsch. Ges. Rostock, new series*, **3**, 267, 315 (1911).
- (34) GALLOIS, N., AND HARDY, E.: *Bull. soc. chim.*, new series, **26**, 39 (1876); *J. pharm. chim.* [4] **24**, 25 (1876).
- (35) GHATAK, N.: *Bull. Akad. Sci. United Provinces Agra, Oudh, Allahabad, India*, **2**, 79 (1932).  
GHATAK, N., AND PENDRE, G. P.: *ibid* **2**, 259 (1933).
- (36) GREENISH, H.: *Pharm. Z. Russland* **20**, 80 (1881); *Chem. Zentr.* **1881**, 218.

- (37) GÜRBER, A.: Münch. med. Wochschr. **58**, 2100 (1911).
- (38) HARNACK, E., AND ZABROCKI, R.: Arch. exptl. Path. Pharmacol. **15**, 403 (1882).
- (39) HARNACK, E.: Arch. Pharm. **234**, 561 (1896).
- (40) HEFFTER, A., AND SACHS, F.: Biochem. Z. **40**, 83 (1912).
- (41) HENNIG: Arch. Pharm. **255**, 382 (1917).
- (42) HERRARA, A.: Pharm. J. **3**, 7, 854 (1876).
- (43) HOMOLLE, E., AND QUEVENNE, T.-A.: Arch. physiol. therap. hygiene (Bou-chardat) Jan. **1854**, 1.
- (44) VON HUSEMANN AND MARMÉ: Ann. **135**, 55 (1865).
- (45) INOKO, Y.: Arch. exptl. Path. Pharmacol. **28**, 302 (1891).
- (46) JACOBS, W. A.: J. Biol. Chem. **88**, 519 (1930).
- (47) JACOBS, W. A.: Physiol. Rev. **13**, 222 (1933).
- (48) JACOBS, W. A., AND BIGELOW, N. M. J. Biol. Chem. **99**, 521 (1933).
- (49) JACOBS, W. A., AND BIGELOW, N. M. J. Biol. Chem. **96**, 355 (1932).
- (50) JACOBS, W. A., AND BIGELOW, N. M. J. Biol. Chem. **96**, 647 (1932).
- (51) JACOBS, W. A., AND BIGELOW, N. M. J. Biol. Chem. **101**, 15 (1933).
- (52) JACOBS, W. A., AND BIGELOW, N. M. J. Biol. Chem. **101**, 697 (1933).
- (53) JACOBS, W. A., AND COLLINS, A. M. J. Biol. Chem. **59**, 713 (1924).
- (54) JACOBS, W. A., AND COLLINS, A. M. J. Biol. Chem. **61**, 387 (1924).
- (55) JACOBS, W. A., AND COLLINS, A. M. J. Biol. Chem. **63**, 123 (1925).
- (56) JACOBS, W. A., AND COLLINS, A. M. J. Biol. Chem. **64**, 383 (1925).
- (57) JACOBS, W. A., AND COLLINS, A. M. J. Biol. Chem. **65**, 491 (1925).
- (58) JACOBS, W. A., AND ELDERFIELD, R. C.: J. Biol. Chem. **91**, 625 (1931).
- JACOBS, W. A., ELDERFIELD, R. C., GRAVE, T. B., AND WIGNALL, E. W.: J. Biol. Chem. **91**, 617 (1931).
- (59) JACOBS, W. A., AND ELDERFIELD, R. C. J. Biol. Chem. **92**, 313 (1931).
- (60) JACOBS, W. A., AND ELDERFIELD, R. C. J. Biol. Chem. **96**, 357 (1932).
- (61) JACOBS, W. A., AND ELDERFIELD, R. C. J. Biol. Chem. **97**, 727 (1932).
- (62) JACOBS, W. A., AND ELDERFIELD, R. C. J. Biol. Chem. **99**, 693 (1933).
- (63) JACOBS, W. A., AND ELDERFIELD, R. C. J. Biol. Chem. **100**, 671 (1933).
- (64) JACOBS, W. A., AND ELDERFIELD, R. C. J. Biol. Chem. **102**, 237 (1933).
- (65) JACOBS, W. A., AND ELDERFIELD, R. C.: J. Biol. Chem. **108**, 497 (1935); Science **80**, 434 (1934).
- (66) JACOBS, W. A., AND ELDERFIELD, R. C.: J. Biol. Chem. **108**, 693 (1935).
- (67) JACOBS, W. A., AND ELDERFIELD, R. C.: In press.
- (68) JACOBS, W. A., ELDERFIELD, R. C., HOFFMANN, A., AND GRAVE, T. B.: J. Biol. Chem. **93**, 127 (1931).
- (69) JACOBS, W. A., AND GUSTUS, E. L. J. Biol. Chem. **74**, 805 (1927).
- (70) JACOBS, W. A., AND GUSTUS, E. L. J. Biol. Chem. **74**, 811 (1927).
- (71) JACOBS, W. A., AND GUSTUS, E. L. J. Biol. Chem. **74**, 829 (1927).
- (72) JACOBS, W. A., AND GUSTUS, E. L. J. Biol. Chem. **74**, 795 (1927).
- (73) JACOBS, W. A., AND GUSTUS, E. L. J. Biol. Chem. **78**, 573 (1928).
- (74) JACOBS, W. A., AND GUSTUS, E. L. J. Biol. Chem. **79**, 539 (1928).
- (75) JACOBS, W. A., AND GUSTUS, E. L.: J. Biol. Chem. **79**, 553 (1928); **82**, 403 (1929); **88**, 531 (1930).
- (76) JACOBS, W. A., AND GUSTUS, E. L.: J. Biol. Chem. **84**, 183 (1929).
- (77) JACOBS, W. A., AND GUSTUS, E. L.: J. Biol. Chem. **86**, 199 (1930).
- (78) JACOBS, W. A., AND GUSTUS, E. L.: J. Biol. Chem. **88**, 531 (1930).
- (79) JACOBS, W. A., AND GUSTUS, E. L.: J. Biol. Chem. **92**, 323 (1931).
- (80) JACOBS, W. A., AND HEIDELBERGER, M.: J. Biol. Chem. **54**, 253 (1922).
- (81) JACOBS, W. A., AND HEIDELBERGER, M.: J. Biol. Chem. **81**, 765 (1929).

- (82) JACOBS, W. A., AND HOFFMANN, A. J. Biol. Chem. **67**, 333 (1926).
- (83) JACOBS, W. A., AND HOFFMANN, A. J. Biol. Chem. **67**, 609 (1926).
- (84) JACOBS, W. A., AND HOFFMANN, A. J. Biol. Chem. **69**, 153 (1926).
- (85) JACOBS, W. A., AND HOFFMANN, A. J. Biol. Chem. **74**, 788 (1927).
- (86) JACOBS, W. A., AND HOFFMANN, A. J. Biol. Chem. **79**, 519 (1928).
- (87) JACOBS, W. A., AND HOFFMANN, A. J. Biol. Chem. **79**, 531 (1928).
- (88) JACOBS, W. A., HOFFMANN, A., AND GUSTUS, E. L.: J. Biol. Chem. **70**, 1 (1926).
- (89) JENSEN, H., AND CHEN, K. K.: J. Biol. Chem. **87**, 741 (1930).
- (90) JENSEN, H., AND CHEN, K. K.: J. Biol. Chem. **87**, 755 (1930).
- (91) JENSEN, H.: Science **76**, 53 (1932).
- (92) JENSEN, H., AND EVANS, E. A., JR.: J. Biol. Chem. **104**, 307 (1934).
- (93) KAMERMAN, P.: South African J. Sci. **23**, 179 (1926).
- (94) KARRER, W.: Helv. Chim. Acta **12**, 506 (1929).
- (95) KARSTEN, W.: Ber. deut. pharm. Ges. **12**, 245 (1902).
- (96) KELLER, O.: Arch. Pharm. **248**, 463 (1910).
- (97) KIEFER, H.: Schweiz. Apoth. Ztg. **60**, 561 (1922).
- (98) KILIANI, H.: Arch. Pharm. **233**, 299, 698 (1895); **237**, 455 (1899); **252**, 26 (1914); Ber. **31**, 2454 (1898); **34**, 3561 (1901).
- (99) KILIANI, H.: Arch. Pharm. **234**, 446 (1896); Ber. **43**, 3574 (1910); **46**, 667, 2179 (1913).
- (100) KILIANI, H.: Arch. Pharm. **233**, 311 (1895); **234**, 273, 481 (1896); **235**, 425 (1897); **237**, 446 (1899); Ber. **32**, 2196 (1899).
- (101) KILIANI, H.: Arch. Pharm. **234**, 481 (1896); **237**, 450 (1899).
- (102) KILIANI, H.: Arch. Pharm. **234**, 319 (1895).
- (103) KILIANI, H.: Arch. Pharm. **234**, 486 (1896).
- (104) KILIANI, H.: Ber. **32**, 2196 (1899).
- (105) KILIANI, H.: Ber. **38**, 4040 (1905).
- (106) KILIANI, H.: Ber. **55**, 88 (1922).
- (107) KILIANI, H.: Ber. **25**, 2116 (1892).
- (108) KILIANI, H.: Ber. **38**, 3621 (1905); **55**, 92 (1922); **64**, 2027 (1931).
- (109) KILIANI, H.: Arch. Pharm. **251**, 562 (1913); **252**, 13 (1914); Ber. **48**, 334 (1915).
- (110) KILIANI, H., AND WINDAUS, A.: Arch. Pharm. **237**, 458 (1899).
- (111) KODAMA, K.: Acta Schol. Med. Univ. Imp. Kioto **3**, 299 (1920).
- (112) KONDO, H., AND IKAWA, S.: J. Pharm. Soc. Japan **53**, 2 (1933); Chem. Zentr. **1933**, I, 2558.
- (113) KONDO, H., AND IKAWA, S.: J. Pharm. Soc. Japan **53**, 62 (1933); Chem. Zentr. **1933**, II, 723.
- (114) KONDO, H., AND IKAWA, S.: J. Pharm. Soc. Japan **54**, 22 (1934); Chem. Zentr. **1934**, I, 3753.
- (115) KOTAKE, M.: Ann. **465**, 11 (1928); Sci. Papers Inst. Phys. Chem. Research Tokyo **9**, 233 (1928).
- (116) KOTAKE, M.: Ann. **465**, 1 (1928).
- (117) KRAFFT, F.: Arch. Pharm. **250**, 126 (1912).
- (118) KRAUSSE, M.: Berlin. klin. Wochschr. **47**, 1699 (1910).
- (119) KROMER, N.: Arch. Pharm. **234**, 452 (1896).
- (120) LEHMANN, E.: Arch. Pharm. **235**, 157 (1897).
- (121) LEULIER, A.: J. pharm. chim. [7] **4**, 157 (1911); [7] **5**, 108 (1912).
- (122) LEVENE, P. A., AND MORI, T.: J. Biol. Chem. **83**, 803 (1929).  
LEVENE, P. A., AND LONDON, E. S.: J. Biol. Chem. **81**, 711 (1929); **83**, 793 (1929).
- (123) LEWIN, L.: Die Pfeilgifte. Verlag von Johann Ambrosius Barth, Leipzig (1923).

- (124) LINDNER, J.: *Monatsh.* **36**, 257 (1915).  
(125) LINDNER, J., AND TORGGLER, A.: *Monatsh.* **63**, 335 (1934).  
(126) MANNICH, C., MOHS, P., AND MAUSS, W.: *Arch. Pharm.* **268**, 453 (1930).  
(127) MAPLETHORPE, C. W.: *Pharm. J.* **111**, 85 (1923).  
(128) MERCIER, L. J.: *Bull. gen. therap.* **168**, 133 (1914); *Schweiz. Apoth. Ztg.* **67**, 301 (1929).  
(129) MERCIER, L. J., AND MERCIER, F.: *Rev. pharmacol. therap. exp.* **1**, 1 (1927).  
(130) MICHEEL, F.: *Ber.* **63**, 347 (1930).  
(131) MINKIEWICZ, M.: *Arb. Pharm. Inst. Dorpat.* **5**, 127 (1890); *Zentr. med. Wiss.* **29**, 44 (1891).  
(132) MOORE, B., SOWTON, S. C. M., BAKER-YOUNG, F. W., AND WEBSTER, T. A.: *Biochem. J.* **5**, 94 (1911).  
(133) MORDAGNE, J.: *Ber.* **18**, 566R (1885).  
(134) MULDER: *Ann.* **28**, 304 (1838).  
(135) NATIVELLE: *J. pharm. chim.* [4] **9**, 255 (1869).  
(136) OLIVIER, C. P., AND HENRY, FILS: *Arch. gen. Med.* **4**, 351 (1824).  
(137) PASCHKIS, H.: *Zentr. med. Wiss.* **30**, 162, 193 (1892).  
(138) PELLETIER AND CAVENTOU: *Ann. chim. phys.* [2] **26**, 44 (1824).  
(139) PERROT, E., AND LEPRINCE, M.: *Compt. rend.* **149**, 1393 (1909).  
(140) PETRIE, J. M.: *Proc. Linnean Soc. N. S. Wales* **46**, 333 (1921).  
(141) PIESZCZEK, E.: *Arch. Pharm.* **228**, 352 (1890).  
(142) PLUGGE, P. C.: *Arch. Pharm.* **231**, 10 (1893).  
(143) PLUGGE, P. C.: *Arch. intern. pharmacodynamie* **2**, 538 (1896).  
(144) POWER, F. B., AND SALWAY, A. H.: *Am. J. Pharm.* **84**, 237 (1912).  
(145) PRESCOTT, A. B.: *Am. J. Pharm.* **50**, 563 (1878).  
(146) PROCTOR: *Pharm. J.* **16**, 233 (1856).  
(147) ROGERSON, H.: *J. Chem. Soc.* **101**, 1040 (1912).  
(148) SCHLAGDENHAUFFEN AND REEB: *Arch. intern. pharmacodynamie* **3**, 5 (1897).  
(149) SCHMIDT, O. T., AND ZEISER, H.: *Ber.* **67**, 2127 (1934).  
(150) SCHMIEDEBERG, O.: *Arch. exptl. Path. Pharmacol.* **3**, 27 (1875).  
(151) SCHMIEDEBERG, O.: *Arch. exptl. Path. Pharmacol.* **16**, 162 (1883).  
(152) SHIMIZU, S.: *J. Pharm.* **8**, 347 (1916).  
(153) SIEBURG, E.: *Arch. Pharm.* **251**, 154 (1913).  
(154) SMITH, S.: *J. Chem. Soc.* **1930**, 508; **1931**, 23.  
(155) STOLL, A., HOFFMANN, A., AND HELFENSTEIN, A.: *Helv. Chim. Acta* **18**, 644 (1935).  
(156) STOLL, A., HOFFMANN, A., AND HELFENSTEIN, A.: *Helv. Chim. Acta* **17**, 641 (1934).  
STOLL, A., AND HOFFMANN, A.: *Helv. Chim. Acta* **18**, 82 (1935).  
(157) STOLL, A., HOFFMANN, A., AND KREIS, W.: *Helv. Chim. Acta* **17**, 1334 (1934).  
STOLL, A., AND HOFFMANN, A.: *Helv. Chim. Acta* **18**, 401 (1935).  
(158) STOLL, A., AND KREIS, W.: *Helv. Chim. Acta* **18**, 120 (1935).  
(159) STOLL, A., AND KREIS, W.: *Helv. Chim. Acta* **16**, 1049, 1390 (1933); **17**, 592 (1934).  
(160) STOLL, A., KREIS, W., AND HOFFMANN, A.: *Z. physiol. Chem.* **222**, 24 (1933).  
(161) STOLL, A., SUTER, E., KREIS, W., BUSSEMAKER, B. B., AND HOFFMANN, A.: *Helv. Chim. Acta* **16**, 703 (1933).  
(162) STRAUB, W.: *Arch. exptl. Path. Pharmacol.* **80**, 52 (1916).  
(163) TAHARA, Y.: *Ber.* **24**, 2579 (1891).  
(164) TANRET: *Jahresber. Chem.* **1882**, 1130.  
(165) TANRET, G.: *Bull. soc. chim. biol.* **14**, 708 (1932).

- (166) TANRET, G.: Bull. soc. chim. biol. **16**, 941 (1934); Compt. rend. **196**, 1637 (1934).  
(167) TAUBER, H., AND ZELLNER, J.: Arch. Pharm. **264**, 689 (1926).  
(168) THAETER, K.: Arch. Pharm. **235**, 414 (1897).  
(169) THOMS, H.: Ber. pharm. Ges. **14**, 114 (1904).  
(170) TSCHESCHE, R.: Z. physiol. Chem. **222**, 50 (1933).  
(171) TSCHESCHE, R.: Z. physiol. Chem. **229**, 219 (1934); Z. angew. Chem. **47**, 729 (1934).  
(172) TSCHESCHE, R.: Ber. **68**, 7 (1935).  
(173) TSCHESCHE, R.: Ber. **68**, 423 (1935).  
(174) TSCHESCHE, R., AND KNICK, H.: Z. physiol. Chem. **222**, 58 (1933).  
(175) TSCHESCHE, R., AND KNICK, H.: Z. physiol. Chem. **229**, 233 (1934).  
(176) VOTACEK AND VONDRACEK: Ber. **36**, 4372 (1904).  
(177) WALZ, G. F.: Neues Jahrb. Pharm. **10**, 145 (1858).  
(178) WEITZ, R., AND BOULAY, A.: Bull. soc. pharmacol. **30**, 81 (1923); Compt. rend. soc. biol. **87**, 1105 (1922).  
(179) WENZEL, W. E.: Am. J. Pharm. **34**, 385 (1862).  
(180) WIELAND, H., AND ALLES, R.: Ber. **55**, 1789 (1922).  
(181) WIELAND, H., AND DANE, E.: Z. physiol. Chem. **210**, 268 (1932).  
(182) WIELAND, H., AND HESSE, G.: Ann. **517**, 22 (1935).  
(183) WIELAND, H., HESSE, G., AND MEYER, H.: Ann. **493**, 272 (1932).  
(184) WIELAND, H., SCHLICHTING, O., AND JACOBI, R.: Z. physiol. Chem. **161**, 80 (1926).  
(185) WIELAND, H., AND VOCKE, F.: Ann. **481**, 215 (1930).  
(186) WIELAND, H., AND WEIL, F. J.: Ber. **46**, 3315 (1913).  
WIELAND, H., AND WEYLAND, P.: Sitzber. math. physik. Klasse bayer. Akad. Wiss. München **1920**, 329.  
(187) WINDAUS, A.: Nachr. Ges. Wiss. Göttingen. Math. physik. Klasse **1926**, 170.  
WINDAUS, A., AND STEIN, G.: Ber. **61**, 2436 (1928).  
(188) WINDAUS, A.: Nachr. Ges. Wiss. Göttingen. Math. physik. Klasse **1927**, 422.  
(189) WINDAUS, A.: Nachr. Ges. Wiss. Göttingen. Math. physik. Klasse **1928**, 3.  
(190) WINDAUS, A.: Arch. exptl. Path. Pharmacol. **135**, 253 (1928).  
(191) WINDAUS, A., AND BANDTE, G.: Ber. **56**, 2001 (1923).  
WINDAUS, A., BOHNE, A., AND SCHWIEGER, A.: Ber. **57**, 1388 (1924).  
WINDAUS, A., AND FREESE, C.: Ber. **58**, 2503 (1925).  
(192) WINDAUS, A., AND HAACK, E.: Ber. **63**, 1377 (1930).  
(193) WINDAUS, A., AND HERMANN, L.: Ber. **48**, 993 (1915).  
(194) WINDAUS, A., AND SCHWARTE, G.: Ber. **58**, 1515 (1925).  
(195) WINDAUS, A., AND SCHWARTE, G.: Nachr. Ges. Wiss. Göttingen. Math. physik. Klasse **1926**, 1.  
(196) WINDAUS, A., AND WESTPHAL, K.: Nachr. Ges. Wiss. Göttingen. Math. physik. Klasse **1925**, 78.  
(197) WINDAUS, A., WESTPHAL, K., AND STEIN, G.: Ber. **61**, 1847 (1928).  
(198) WOLFF: Inaugural Dissertation, Marburg, 1925.



# STERNUTATORS<sup>1</sup>

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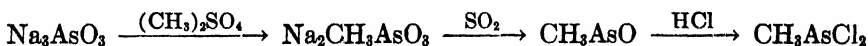
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## INTRODUCTION

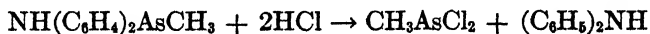
Among the chemical agents which have been most frequently employed because of their sternutatory properties are methyldichloroarsine, ethyldichloroarsine, diphenylcyanoarsine, diphenylchloroarsine, and diphenylaminechloroarsine.

### I. METHYLDICHLOROARSINE, DICHLOROMETHYLARSINE, $\text{CH}_3\text{AsCl}_2$

Bayer (9) prepared methyldichloroarsine by warming cacodyl trichloride to 40–50°C. and by the action of hydrochloric acid on cacodylic acid. Uhling and Cook (143) prepared it by methylating a solution of sodium arsenite with dimethyl sulfate at 85°C., then reducing the disodium methyl arsenite to methylarsine oxide by means of sulfur dioxide, and finally converting the oxide to methyldichloroarsine by passing hydrogen chloride through the oil:



Auger (5) obtained methyldichloroarsine by adding methylarsinic acid to cooled phosphorus trichloride; also by the action of chlorine on methylarsine (4). Gibson and Johnson (53) obtained it by decomposing 10-methyl-5, 10-dihydrophenarsazine with dry hydrogen chloride at 110–130°C.:



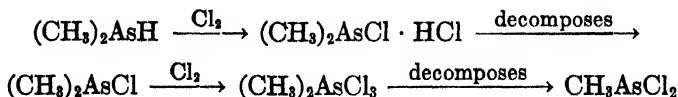
By treating sodium dimethylarsenate with concentrated hydrochloric acid (density 1.19) (155, 156); by dissolving cacodylic acid in concentrated hydrochloric acid and saturating with hydrogen chloride (9, 151); by the hydrolysis of dimethyltrichloroarsine (151).

It was thought by Dehn and Wilcox (35) and by Palmer (101) that probably chlorine reacts with dimethylarsine with the formation of chloro-

<sup>1</sup>This is the fifth in a series of five articles on chemical warfare materials. For preceding articles see Chem. Rev. 14, 251 (1934); 15, 425 (1935); 16, 195, 439 (1935).—*Editor*.



cacodyl hydrochloride which decomposes at the temperature of the reaction and forms cacodyl chloride; this could then react with chlorine with the formation of the pentavalent body, dimethylarsinetrichloride,  $(\text{CH}_3)_2\text{AsCl}_3$ , which decomposes at a temperature above  $40\text{--}50^\circ\text{C.}$  with the formation of methylchloroarsine:



### Physical properties

Methylchloroarsine is a colorless, heavy, mobile, strongly refractive liquid, boiling at  $37^\circ\text{C.}$  at 25 mm. (66),  $55.5^\circ\text{C.}$  at 50 mm. (53),  $72.1^\circ\text{C.}$  at 100 mm. (53),  $89.1^\circ\text{C.}$  at 200 mm. (53),  $109.1^\circ\text{C.}$  at 400 mm. (53),  $123^\circ\text{C.}$

TABLE 1

Vapor pressure of methylchloroarsine

$$\log \text{vapor pressure} = 8.6944 - 2281.7/273 + t$$

TEMPERATURE	VAPOR PRESSURE OBSERVED	VAPOR PRESSURE CALCULATED	DIFFERENCE CALCULATED - OBSERVED
$^\circ\text{C.}$	mm.	mm.	mm.
35	19.33	19.33	0.00
25	10.83	10.90	+0.07
15	5.94	5.91	-0.03
0	2.17	2.17	0.00
-15	0.67	0.71	+0.04
-16.8	0.56	0.61	+0.05
-17	0.53	0.60	+0.07

(35),  $130\text{--}132^\circ\text{C.}$  (155, 156),  $131.8\text{--}132.4^\circ\text{C.}$  at 12 mm. (63),  $132^\circ\text{C.}$  (151),  $132.5^\circ\text{C.}$  (53),  $133^\circ\text{C.}$  (5, 9, 66, 83, 95). It is somewhat soluble in water but more soluble in the usual organic solvents.  $d_4^{20}$ , 1.8358 (vacuum) (53);  $d_4^{20}$ , 1.8380 (83);  $d_4^{15.6}$ , 1.8471 (63). Its volatility at  $20^\circ\text{C.}$  amounts to 75 grams per cubic meter (3, 95). Its vapor tension at  $25^\circ\text{C.}$  is 10.83 mm. (83). The molecular heat of vaporization and Trouton's constant at 760 mm. are calculated as 7890 calories and 19.4 (53). Its index of refraction at  $14.5^\circ\text{C.}$  is as follows:  $n_\alpha = 1.5624$ ,  $n_D = 1.5677$ ,  $n_\beta = 1.5814$ ,  $n_\gamma = 1.5933$  (63). The molecular refraction values for the D line of sodium and the  $\alpha$ ,  $\beta$ , and  $\gamma$  hydrogen lines are, respectively, 28.50, 28.28, 29.06, and 29.35 (63).

Baxter, Bezzenberger, and Wilson (12) determined the vapor pressure of methylchloroarsine by the "air current" or "transference" method. A known volume of air, as determined by the measured volume of water

run out of an aspirator, was saturated with the vapor of methyldichloroarsine by passing through a weighed receptacle maintained at constant temperature in a water thermostat. The loss in weight of the saturating tube furnished the weight of evaporated substance. From the latter quantity the volume of vapor was calculated on the assumption that the volume of a gram-molecule under standard conditions is 22.4 liters. The per cent of vapor by volume multiplied by the interior pressure, as determined by the barometric reading and an open-arm manometer attached to the aspirator, gives the vapor pressure. The control of the temperature in the thermostat was within  $0.1^{\circ}\text{C}$ .

A plot of the logarithm of the vapor pressure against the reciprocal of the absolute temperature gives a very nearly straight line, which, therefore, can be represented by an empirical equation of the form:

$$\log \text{vapor pressure} = A + B/273 + t$$

Vapor pressures calculated by means of these equations agree with the observed values within the experimental error. For a higher degree of accuracy the equations were not adequate, however, and can not be trusted for extrapolation over any considerable range.

### *Chemical properties*

(a) *Reduction.* Upon reduction of methyldichloroarsine, methylarsine is formed (32, 101, 102).

(b) *Action with metals.* Magnesium does not act on methyldichloroarsine even when boiled in the presence of anhydrous ether, but when water is added the two react violently, giving essentially monomethylarsine, methylarsenide,  $(\text{CH}_3\text{As})_x$ , being precipitated, and magnesium chloride left in solution. Zinc produces a similar decomposition (154).

(c) *Action with chlorine.* Upon passing chlorine into a carbon disulfide solution of methyldichloroarsine cooled to  $-10^{\circ}\text{C}$ ., methylarsenic tetrachloride,  $\text{CH}_3\text{AsCl}_4$ , forms as large crystals (9); it decomposes at  $0^{\circ}\text{C}$ . to methyl chloride and arsenic trichloride.

(d) *Action with hydrogen sulfide.* Upon passing hydrogen sulfide into methyldichloroarsine, methylarsenious sulfide,  $\text{CH}_3\text{AsS}$ , is formed (9); it smells of asafœtida, and forms in yellow crystals, m.p.  $95^{\circ}\text{C}$ .

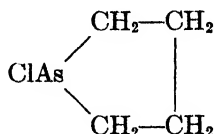
(e) *Action with potassium hydroxide.* Upon heating methyldichloroarsine with potassium hydroxide there is formed methylarseno oxide,  $\text{CH}_3\text{AsO}$ , yellow crystals, m.p.  $95^{\circ}\text{C}$ .; this compound smells of asafœtida (9).

(f) *Action with chloropicrin.* Methylarsenic acid,  $\text{CH}_3\text{AsO}(\text{OH})_2$ , obtained by treating the sodium salt (from treating methyldichloroarsine with

sodium ethoxide) with chloropierin, crystallizes from alcohol in colorless plates melting at 132–133°C. (150)

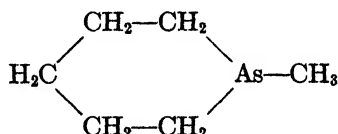
(g) *Action with isoamyl chloride.* When an ethereal solution of methyldichloroarsine is treated with a similar solution of isoamylmagnesium chloride (in an atmosphere of nitrogen) there is formed methyldiisoamyl arsine,  $\text{CH}_3(\text{C}_6\text{H}_{11})_2\text{As}$ , a liquid boiling at 95–96°C. at 11 mm. (129).

(h) *Action with  $\alpha, \epsilon$ -dibromopentane.* (1) Cyclotetramethylenearsine chloride,

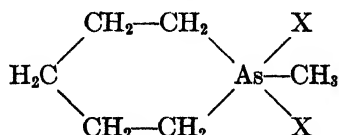


The Grignard reagent prepared from  $\alpha, \epsilon$ -dibromopentane in ether with magnesium is cooled and treated with methyldichloroarsine; the product, decomposed with hydrochloric acid and with chlorine, forms a clear liquid, boiling at 77°C. at 18 mm. (131).

(2) Methylcyclopentamethylene arsine, 1-methylarsepedine,



appears to be the first case of a heterocyclic compound with arsenic in the ring. Methyldichloroarsine added to the Grignard reagent prepared from  $\alpha, \epsilon$ -dichloropentane, magnesium, and methyl iodide in ether forms a colorless liquid, boiling at 160°C., and possessing the odor of mustard oil. It is insoluble in water and hydrochloric acid, but soluble in alcohol, ether, petroleum ether, benzene, and carbon tetrachloride. It is volatile with steam. It is not combustible, but when poured upon filter paper it causes the latter to inflame and clouds of arsenious oxide vapor are given off. In contact with air it is oxidized with formation of the oxide, which is colorless and possesses a more agreeable odor than the cycloarsine. It reduces ammoniacal silver nitrate and alkaline permanganate solutions. It combines additively with halogens (152) giving compounds of the type



It boils at 156°C. (153), 76°C. at 36 mm. (153), 65°C. at 20–22 mm. (153), 57–58°C. at 20 mm. (60).  $d_4^{20}$ , 1.2180 (153).

*Test*

When a few drops of mercurous nitrate are brought in contact with methyldichloroarsine, a dark gray precipitate containing metallic mercury is formed (97).

*Physiological properties*

Methyldichloroarsine has a very irritating effect on the mucous membrane. Hyperemia, swelling, edema, ulceration, and necrosis take place on the skin of the dog, and similar changes, together with vesication, take place on human skin (64).

II. ETHYLDICHLOROARSINE, DICHLOROETHYLARSINE,  $C_2H_5AsCl_2$ *Preparation*

Ethyldichloroarsine was first prepared by LaCoste in 1881 (73) and later by Steinkopf and Mieg (130) by treating mercury diethyl with arsenic trichloride. Dehn (33) found that when ethylarsine, in a sealed tube, was treated with any one of the following chlorides—mercury (ic), phosphorus (ous), tin (ous), arsenic (ous), or antimony (ous)—ethyldichloroarsine was obtained. It results when arsenic trichloride reacts with ethyl magnesium bromide at low temperature (6). McKenzie and Wood (84) prepared ethyldichloroarsine by first preparing ethyldiiodoarsine from ethyl iodide and a sodium hydroxide solution of arsenious oxide, through which sulfur dioxide was passed until the iodine color was removed. The ethyliodoarsine was then changed to the oxide with calcium chloride and anhydrous sodium carbonate, and the oxide converted to the chloride by passing in hydrogen chloride. Norris (99) prepared the chloroarsine by treating ethylarsenious oxide with hydrochloric acid. Arsenious oxide was combined with ethyl chloride at 100°C. with vigorous stirring to form ethylarsenious oxide; the oil was then chlorinated at 12 atmospheres and finally treated with sulfuric acid and sodium sulfite (26). It has also been prepared by the decomposition of 10-ethyl-5,10-dihydrophenarsazine with dry hydrogen chloride at 110–130°C. (53).

*Physical properties*

Ethyldichloroarsine is a clear, colorless liquid having a faint, fruity odor. It is slightly soluble in water and miscible in all proportions with alcohol, ether, and benzene (73). Its boiling point has been reported as 21.5°C. at 2.295 mm. (66), 74°C. at 74 mm. (53), 90°C. at 100 mm. (53), 109.6°C. at 200 mm. (53), 131.2°C. at 400 mm. (53), 145–150°C. (83, 130), 152.5–153.5°C. (63), 153°C. (66), 153–156°C. (137), 155.3°C. (53), 156°C. (3, 33, 57, 73, 123). Its vapor pressure at 20°C. is 0.022 mm. (137).  $d_4^{20}$  (vacuum), 1.6595 (53);  $d_4^{20}$ , 1.7420 (63). Its volatility at 0°C. is 5.08 g. per

cubic meter (137). At 21.5°C. 22 g. saturates 1 cubic meter (3). Its molecular heat of vaporization and Trouton's constant at 760 mm. are calculated as 9180 calories and 21.4 (53). Its index of refraction at 14.5°C. has been reported as follows:  $n_\alpha = 1.5537$ ,  $n_D = 1.5588$ ,  $n_\beta = 1.5713$ ,  $n_\gamma = 1.5820$  (63). The molecular refraction values for the D line of sodium and the  $\alpha$ ,  $\beta$ , and  $\gamma$  hydrogen lines are, respectively, 32.42, 32.18, 33.02, and 33.53 (63).

### Chemical properties

(a) *Action with nitric acid.* Ethylarsinic acid,  $C_2H_5AsO(OH)_2$ , is obtained from ethyldichloroarsine by prolonged warming with dilute nitric acid (34, 73). It crystallizes in needles, m.p. 95–96°C. One hundred parts of water dissolve 70 parts of the acid at 27°C. and 112 parts at 40°C.; 100 parts of 96 per cent alcohol dissolve 70 parts of the acid at 25°C. (34).

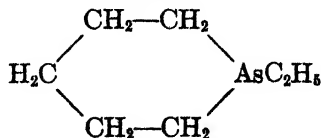
(b) *Action with sodium iodide.* Ethyliodoarsine,  $C_2H_5AsI_2$ , is prepared by the interaction of ethyldichloroarsine and sodium iodide in dry acetone solution; the product boils at 122.7°C. at 11 mm. (133). It is a reddish-yellow oil, boiling at 126°C. at 11 mm., and separates as a pale crystalline solid melting at –9°C. on cooling in solid carbon dioxide (20).

(c) *Action with hydrogen sulfide.* Ethylarsino sulfide,  $C_2H_5AsS$ , is prepared by the action of hydrogen sulfide on an alcoholic solution of ethyldichloroarsine. It is a yellow oil with an offensive odor. It is soluble in carbon disulfide and chloroform.  $d_{20}^{20}$ , 1.8218 (72).

(d) *Action with potassium carbonate.* Ethylarsine oxide,  $C_2H_5AsO$ , is obtained by treating ethyldichloroarsine with a benzene solution of potassium carbonate and fractionating *in vacuo*, all reactions taking place in carbon dioxide. It is colorless oil, boiling at 158°C. at 10 mm.; it is soluble in benzene, ether, and acetone (130).

(e) *Action with alkyl halides.* Ethyldipropylarsine,  $C_2H_5[(C_3H_7)]_2As$ , prepared by treating the Grignard solution obtained from propyl bromide and magnesium in ether with an ethereal solution of ethyldichloroarsine, is a highly refractive liquid boiling at 60–64°C. at 14 mm. (127). Ethyldiisobutylarsine,  $C_2H_5[(CH_3)_2CH \cdot CH]_2As$ , prepared by treating the Grignard solution obtained from isobutyl bromide and magnesium in ether with an ethereal solution of ethyldichloroarsine, is a strongly refractive liquid boiling at 86°C. at 16 mm. (127).

(f) *Action with  $\alpha, \epsilon$ -dibromopentane.* Cyclopentamethyleneethylarsine,



prepared by treating two molecules of the cooled Grignard solution of  $\alpha$ , $\epsilon$ -dibromopentane in ether with one molecule of an ethereal solution of ethyldichloroarsine, has a not unpleasant, more ethereal than arsine-like odor when fresh, but develops the typical arsine odor in a day. It boils at 62–64°C. at 12.5 mm. (127).

(g) *Action with ethyl bromide.* Diethylarsinic acid, ethylcacodylic acid,  $(C_2H_5)_2AsOOH$ , is prepared by warming ethyl bromide for four to six hours with ethyldichloroarsine and sodium hydroxide. The large glistening plates have an acid reaction, are odorless, have a bitter taste, melt at 190°C. and are very deliquescent in air. The compound is easily soluble in water and alcohol, the solutions liberating carbon dioxide from alkali carbonates; it is unattacked by concentrated nitric acid or aqua regia (76, 77, 104).

(h) *Action with chloropicrin.* Ethylarsinic acid,  $C_2H_5AsO(OH)_2$ , is obtained by treating the sodium salt (prepared by reaction of sodium ethoxide on ethyldichloroarsine) with chloropicrin; it forms colorless needles, melting at 98–99°C. (150).

(i) *Action with ethyl- $\beta$ -bromoethyl sulfide.* Ethyl( $\beta$ -ethylsulfonyl)ethyl) arsinic acid,  $C_2H_5AsOOHC_2H_4SO_2C_2H_5$ . The sodium salt of this acid is obtained by treating ethyldichloroarsine with sodium ethoxide, then adding slowly ethyl- $\beta$ -bromoethyl sulfide; on acidifying with concentrated hydrochloric acid, the acid separates as colorless, short needles, m.p. 164–165°C., soluble in water, alcohol, almost insoluble in acetone (125).

### Test

When mercurous nitrate solution is added to a solution of ethyldichloroarsine, a white precipitate which turns gray within a few seconds is formed (97).

### Physiological properties

Ethyldichloroarsine is extremely irritating in its action upon the mucous membrane of the nose, eyes, and throat, and causes painful wounds on the skin. It is very dangerous for those working with it, since its vapor causes respiratory embarrassment, faintness and long-lasting paralysis, and anesthesia of the extremities (73).

### III. DIPHENYLCYANOARSINE, CYANODIPHENYLARSINE, $(C_6H_5)_2AsCN$

#### Preparation

Sturniolo and Bellinzoni (138, 139) originally prepared diphenylcyanoarsine, and McKenzie and Wood (84) and others (96, 133) prepared it later by treating diphenylarsenious oxide,  $[(C_6H_5)_2As]_2O$ , or the ethoxy compound (resulting from the treatment of diphenylchloroarsine with sodium ethoxide) with dry hydrogen cyanide. Morgan and Vining (96) prepared

diphenylcyanoarsine by the following methods: (a) by stirring diphenylchloroarsine at 100°C. with 30 per cent hypochlorous acid forming diphenylcacodyl (tetraphenyldiarsine),  $(C_6H_5)_2As-As(C_6H_5)_2$ , which, when heated to 250°C. with mercuric or silver cyanide in a rotating autoclave, produces diphenylcyanoarsine; (b) by heating diphenylarsenious sulfide,  $(C_6H_5)_2As-S-As(C_6H_5)_2$ , with mercuric or silver cyanide for two hours at 160–200°C.; (c) by heating diphenylarsenious chloride, while vigorously stirred, with an excess of dry silver cyanide for three hours at 150–160°C.

Norris (99) prepared diphenylcyanoarsine by vigorously stirring diphenylchloroarsine with a saturated solution of sodium or potassium cyanide at 60°C.; Steinkopf and Schwen (134) prepared it by heating diphenylmethylarsine cyanobromide,  $(C_6H_5)_2CH_2AsBrCN$ , while Steinkopf, Donat, and Jaeger (127) obtained it by heating diphenylethylarsine cyanobromide,  $(C_6H_5)_2C_2H_5AsBrCN$ .

#### *Physical properties*

Diphenylcyanoarsine crystallizes in colorless, monoclinic plates, having the odor of garlic and bitter almonds. Its melting point has been reported as 28–30°C. (96), 30–34°C. (84), 31°C. (133, 145, 147), 31–32°C. (84), 31.5°C. (3, 95, 127, 133, 134, 137), 32–33°C. (63), 32–34°C. (138, 139), 35°C. (83, 138, 139). Its boiling point has been given as 185°C. (146), 191°C. at 10 mm. (66), 192°C. at 14 mm. (137), 192–194°C. at 12 mm. (66), 200–201°C. at 13.5 mm. (133), 204–205°C. at 12 mm. (63), 207–209°C. at 23 mm. (127), 213°C. at 21 mm. (84), 255°C. at 85 mm. (66), 257°C. at 103 mm. (66), over 300°C. (57, 144), 346°C. (3, 95). At 20°C., 0.1–0.15 mg. of it saturates 1 cubic meter of air (3).  $d_{40}^{20}$  1.3160 (63). Its index of refraction at 52°C. is as follows:  $n_\alpha = 1.6092$ ,  $n_D = 1.6153$ ,  $n_\beta = 1.6333$  (63). The molecular refraction values at 52°C. for the D line of sodium and for the  $\alpha$  and  $\beta$  hydrogen lines are, respectively, 67.65, 67.11, and 69.23 (63).

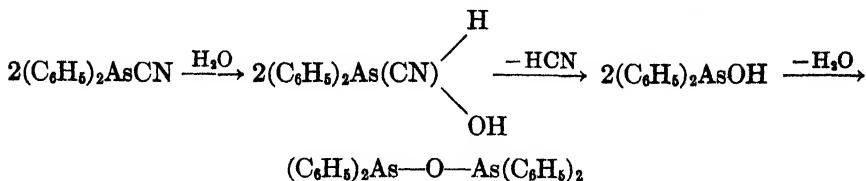
#### *Chemical properties*

(a) *Action with water.* Moist air, acting upon diphenylcyanoarsine, causes the liberation of hydrogen cyanide (138). By treating with water or by heating with water or by distilling in a current of steam or under reduced pressure (100 mm.) the compound is converted into diphenylarsenious oxide.

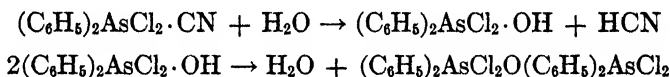
(b) *Action with oxidizing agents.* When heated with concentrated nitric acid on a water bath, or with hydrogen peroxide, or with bromine water, in the cold, diphenylcyanoarsine yields diphenylarsinic acid,  $(C_6H_5)_2AsOOH$  (138).

(c) *Action with alkali.* Diphenylcyanoarsine is very sensitive to alkali-

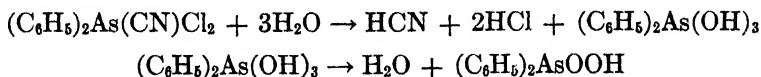
lies, being changed to the oxide easily by even the effect of the alkali of the glass vessel, the reaction occurring in the following stages (84):



(d) *Action with chlorine.* On allowing chlorine to pass into a cooled benzene (or carbon tetrachloride) solution of the cyanoarsine, a solid soon separates; the passage of the halogen is continued until the liquid becomes green in tint. On removal, the solid fumes in air and melts at approximately  $115^\circ\text{C}.$ ; it contains chlorine but no nitrogen. Upon boiling with water it dissolves, and on cooling, needles of diphenylarsinic acid separate. It seems likely that the compound in question is diphenylarsenic oxychloride,  $(\text{C}_6\text{H}_5)_2\text{AsCl}_2-\text{O}-\text{Cl}_2\text{As}(\text{C}_6\text{H}_5)_2$ , produced by the hydrolysis of the cyano group, thus (84):



On allowing the filtrate resulting from the removal of the solid in the above to remain for several days at ordinary temperature, a crystalline product gradually deposits, which softens at  $123^\circ\text{C}.$  and melts at  $127^\circ\text{C}.$  This contains both chlorine and nitrogen and is apparently diphenylcyanoarsine dichloride,  $(\text{C}_6\text{H}_5)_2\text{As}(\text{CN})\text{Cl}_2$ . Once isolated it appears to be fairly stable when dry; when boiled with water, it dissolves completely, and needles of diphenylarsinic acid separate on cooling, as represented by the equations (84):



(e) *Action with methyl iodide.* Diphenyldimethylarsoniumtriiodide,  $(\text{C}_6\text{H}_5)_2\text{As}(\text{CH}_3)_2\text{I}_3$ , results when methyl iodide reacts at  $100^\circ\text{C}.$  with diphenylcyanoarsine. It crystallizes in violet needles, which melt at  $69^\circ\text{C}.$  and are insoluble in water or ether (133).

Job and Guinot (67) obtained French patent 521,469 on July 15, 1921 for the preparation of diphenylarsinecarboxylic acid,  $(\text{C}_6\text{H}_5)_2\text{AsCOOH}$ , by the hydrolysis of diphenylcyanoarsine. By treatment of diphenylarsinecyanide with hydrogen peroxide, or a substance yielding hydrogen peroxide, diphenylarsine formamide,  $(\text{C}_6\text{H}_5)_2\text{AsCONH}_2$ , is formed.



### *Treatment*

Upon bubbling chlorine into solutions of diphenylcyanoarsine, the arsenic is oxidized to the pentavalent form. The resulting products are non-irritating when breathed by men, and give no reaction when titrated with iodine. It was found by Walton and Eldridge (146) that men gassed with diphenylcyanoarsine are markedly benefitted if given chlorine.

### *Physiological properties*

Diphenylcyanoarsine irritates the mucous membrane, provoking sneezing (138). Hanzlik and Tarr (64) found the cyanoarsine to be a mild irritant, as is indicated by simple hyperemia without vesication, mild urticarial rash, moderate swelling and edema, and very little or no necrosis.

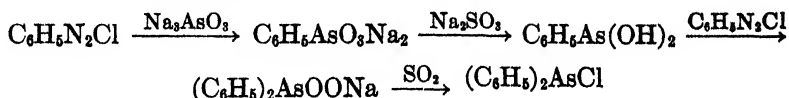
## IV. DIPHENYLARSENIOUS CHLORIDE, DIPHENYLCHLOROARSINE, $(C_6H_5)_2AsCl$

### *Preparation*

Diphenylchloroarsine was first prepared by LaCoste and Michaelis (74) in 1878 by the interaction of mercury diphenyl and arsenic trichloride; the procedure was later modified by Michaelis and coworkers (75, 89, 92). Michaelis has also prepared it by converting triphenylarsine into its dichloride and distilling under 13–14 mm. pressure (90). It has been made by heating triphenylarsine with arsenic trichloride as follows: (1) Pope and Turner (103) prepared it by slowly adding arsenic trichloride dropwise to the triphenylarsine at 350°C. and fractionating the product at 12–15 mm.; (2) Morgan and Vining (96) by heating the triphenylarsine with arsenic trichloride for three hours at 250–280°C. in a rotating autoclave under a pressure of 4.2 to 7 kg. per square centimeter and then fractionating in an atmosphere of carbon dioxide; (3) Oechsli (100) on July 10, 1920 obtained British patent 173,796 for the preparation of diphenylchloroarsine by heating triphenylarsine with arsenic trichloride at 250–350°C. at ordinary pressure. Upon heating phenylarsenious dichloride and triphenylarsine for four hours at 300°C. and distilling the resulting pasty mass under diminished pressure, Pope and Turner (103) were able to obtain nearly pure diphenylarsenious chloride. In view of the possible importance of these reactions, protection was secured by British patent 142,880 on June 11, 1918.

Norris (99) describes the preparation of diphenylchloroarsine as follows: aniline, dissolved in hydrochloric acid, is diazotized with sodium nitrite at 0–5°C., and the resulting benzenediazonium chloride converted into disodium phenylarsonate by condensation with sodium arsenite. This is first transformed into the free arsinic acid by neutralization with hydrochloric acid, and then reduced to phenyldihydroxyarsine (phenylarsenious

acid) by means of sodium sulfite. After dissolving in caustic soda, the dihydroxyarsine is condensed with benzenediazonium chloride to form the sodium salt of diphenylarsinic acid, which is then neutralized with hydrochloric acid, yielding the free arsenic acid. By dissolving in hydrochloric acid and introducing an excess of sulfur dioxide, the diphenylarsinic acid is reduced to diphenylarsenious chloride:



Contardi (29) devised an improvement in the method, which consisted in heating diphenylamine with arsenic trioxide instead of the trichloride. Fused diphenylamine was converted into the hydrochloride by heating with hydrochloric acid (density 1.18) with continuous agitation until the water was almost eliminated, and the residual white powder, dried at 50–60°C., was fused with arsenic trioxide, while being stirred continuously. The heating and stirring was continued for four hours after fusion, during which time the temperature gradually rose to 200°C., the reaction being complete when the evolution of water vapor ceased. Steinkopf, Schubart, and Schmidt (132) prepared the chloride by the reaction of chloroacetyl chloride, carbonyl chloride, phosphorus trichloride, or benzenesulfonyl chloride with diphenylarsine; Blicke, Patelski, and Powers (13) by the action of sulfur chloride, thionyl chloride, arsenic trichloride, phenylarsine oxychloride, or phosphorus trichloride on tetraphenyldiarsyl; Blicke and Powers (15) by the action of phenylchloroethoxyarsine, triphenylarsine dichloride, or triphenylarsine hydroxychloride on diphenylarsine and by the reaction of triphenylarsine dichloride, or triphenylarsine hydroxychloride, on tetraphenyldiarsyl.

Other methods of preparation of diphenylarsenious chloride are accomplished as follows: by gradually adding phenylmagnesium bromide to a large excess of arsenic trichloride in the presence of ether (87); by treating diphenylarsine oxide with an alcoholic solution of hydrochloric acid (90); by boiling benzene with arsenic trichloride (74); by the reduction of diphenylarsinic acid with sulfur dioxide (70); by the reaction between phenyldichloroarsine and diphenylarsine (14); by the Friedel-Crafts reaction using arsenic trichloride and phenyldichloroarsine (147); by heating phosphorus trichloride with triphenylarsine in a sealed tube to 160°C. (27); by the action of aromatic Grignard reagents on arsenic trioxide (16); by the reaction of diphenylarsine with phenyldichloroarsine (128); by the fractional distillation of (a) triphenylchlorodiarsine (128), (b) triphenylarsine dichloride (90), (c) monophenylarsenochloride (89); by the decomposition of diphenylarsenious sulfide with concentrated hydrochloric acid (90); by

the heating of phenylchloroarsine with mercury diphenyl (90); by the action of arsenic trichloride on an ethereal solution of triphenylbismuthine (28); by the reaction of arsenic trichloride on lead tetraethyl (59). Diphenylarsenious chloride is obtained as a by-product in the preparation of triphenylarsine (93, 115); also by the oxidation of (a) phenylhydrazine with pyroarsenic acid in the presence of copper at 75°C., (b) phenylhydrazine arsenate with arsenic acid in the presence of copper at 70°C. (157).

### *Physical properties*

Diphenylchloroarsine is a pale yellow, oily liquid which decomposes upon heating, but in an atmosphere of carbon dioxide boils at the following temperatures: 333°C. (3, 57, 70, 74, 75, 79, 83, 90, 133, 144, 146), 285°C. at 320 mm. (66), 253°C. at 134 mm. (66), 245°C. at 102 mm. (66), 230°C. at 13–14 mm. (133), 224°C. at 55 mm. (66), 218°C. at 48 mm. (66), 214°C. at 42 mm. (66), 211°C. at 38 mm. (66), 205°C. at 30 mm. (66), 193–194°C. at 16 mm. (63), 193°C. at 20 mm. (66), 189°C. at 17 mm. (66), 185°C. at 15 mm. (103), 180°C. at 10 mm. (66), 179–181°C. at 11 mm. (66), 178.6°C. at 10 mm. (57), 172°C. at 7 mm. (65), 161–163°C. at 5 mm. (132). Its melting point has been given as follows: 34°C. (99), 37–38°C. (79), 37–41°C. (13), 37.5°C. (47), 38°C. (3, 83), 38–39°C. (132), 38.5–39.0°C. (43), 39–40°C. (96), 40–41°C. (63), 40–42°C. (15, 16), 41–42°C. (13), 42–43°C. (13), 43°C. (123), 44°C. (57, 146), 44–45°C. (144).

Diphenylchloroarsine exhibits dimorphism: the unstable modification, obtained by spontaneous crystallization of freshly redistilled material or by heating the stable form to 130°C. and cooling under "aseptic" conditions, forms silky needles melting at 18.2–18.4°C., while the stable modification forms rhombic, doubly refracting, biaxial crystals melting at 38.7–38.9°C. (56). The vapor pressure is 0.0001 at 0°C. and 0.0004 at 25°C. (144). The compound has a faint odor at ordinary temperatures; this becomes very irritating when heated. It is soluble in organic solvents, difficultly soluble in aqueous alkalis, and insoluble in water (133).  $d_4^{16}$ , 1.4820 (65);  $d_4^{15}$ , 1.42231 (74, 75, 133);  $d_4^{25}$ , 1.3870 (65);  $d_4^{30}$ , 1.3760 (63);  $d_{10}^{25}$ , 1.3680 (65);  $d_{10}^{30}$ , 1.3500 (65). Its index of refraction at 56°C. is:  $n_\alpha = 1.6256$ ,  $n_D = 1.6332$ ,  $n_\beta = 1.6525$  (63). The molecular refraction values at 56°C. for the D line of sodium and the  $\alpha$  and  $\beta$  hydrogen lines are, respectively, 68.66, 68.01, and 70.32 (63).

Henley and Sugden (65) calculate the parachor of diphenylchloroarsine by the formula:

$$[P] = M\gamma^{1/4} (D - d)$$

where  $M$  = molecular weight,  $\gamma$  = surface tension (dynes per centimeter) determined by the method of maximum bubble pressure, and  $D$  and  $d$  are

densities of liquid and vapor, respectively, which were determined by means of a U-shaped pyknometer.

Baxter, Bezzenberger, and Wilson (12) determined the vapor pressure of diphenylarsenious chloride by the "air current" or "transference" method (table 3).

TABLE 2  
*Parachor of diphenylchloroarsine*

<i>t</i> °C	$\gamma$	<i>D</i>	[ <i>P</i> ]
17 9	45 30	1.411	486.3
42 5	42.65	1 386	487 6
61 0	40.37	1.369	487.0
80 5	38.32	1 350	487.5
Mean value.....			487 1

TABLE 3  
*Vapor pressure of diphenylarsenious chloride*

TEMPERATURE	VAPOR PRESSURE (OBSERVED)	VAPOR PRESSURE (CALCULATED)	DIFFERENCE (CALCULATED - OBSERVED)
°C.	mm	mm	mm
75	0 0282	0.0278	-0.0004
65	0 0148	0 0146	-0 0002
55	0.0065	0 0074	+0.0009
45	0 0039	0 0036	-0.0003
25	0 0003	0 0008	+0 0005

### *Chemical properties*

(a) *Action with water.* Diphenylchloroarsine is hydrolyzed slowly by water forming diphenylarsinic acid,  $(C_6H_5)_2AsOOH$  (74, 75, 89, 90, 116).

(b) *Action with halogens.* With chlorine and bromine, diphenylchloroarsine combines additively, forming the corresponding diphenylarsine trihalides (75, 133). Diphenylchloroarsenic bromide,  $(C_6H_5)_2AsClBr_2$ , and the perbromide,  $(C_6H_5)_2AsClBr_4$ , result when dry bromine is added to cooled diphenylchloroarsine. The former, a yellow crystalline solid, m.p. 158°C. (70), fumes slightly in air and is soluble with partial decomposition in benzene or ether on prolonged boiling (114); the latter forms orange-red crystals, m.p. 150-151°C. (70). On exposure to moist air both bromides lose all the halogen present. When diphenylchloroarsine is treated with dry chlorine, diphenylarsenic chloride,  $(C_6H_5)_2AsCl_3$ , results. It crystallizes from dry benzene in colorless plates, m.p. 174°C.,

and is decomposed by water, forming hydrochloric acid and diphenylarsinic acid (74, 75, 89). Chlorine water oxidizes diphenylarsenious chloride to diphenylarsinic acid (90). The addition of chlorine to diphenylchloroarsine in neutral solution forms diphenylarsine trichloride (dichlorodiphenylarsonium chloride)  $[(C_6H_5)_2AsCl_2]Cl$ , m.p.  $189^\circ C.$ , which on recrystallization from moist acetone is converted into dihydroxydiphenylarsonium chloride,  $(C_6H_5)_2As(OH)_2Cl$  (70).

(c) *Action with metals.* Diphenylchloroarsine is attacked by zinc at  $100^\circ C.$  with the production of a small quantity of a crystalline compound which melts at  $154^\circ C.$  and which dissolves freely in benzene (75).

(d) *Action with acids.* On continued boiling with concentrated nitric acid, diphenylchloroarsine is oxidized to diphenylarsinic acid (70, 75, 133). On boiling with hydrochloric acid diphenylchloroarsine is decomposed with the liberation of arsenic trichloride (112). When the chloroarsine is heated with hypophosphorus acid at  $100^\circ C.$ , diphenylcacodyl (tetraphenyldiarsine),  $(C_6H_5)_2As-As(C_6H_5)_2$ , is formed (96). When diphenylchloroarsine is treated with chlorosulfonic acid there are formed colorless prisms of the compound having the formula,  $2[(C_6H_5)_2AsO(OH)] \cdot HCl$ , m.p.  $114^\circ C.$ , the substance,  $(C_6H_5)_2AsO(OH) \cdot HCl$ , m.p.  $110-130^\circ C.$ , and benzenesulfonyl chloride,  $C_6H_5SO_2Cl$  (132). When diphenylchloroarsine is treated with fluorosulfonic acid there is formed the compound  $2[(C_6H_5)_2AsO(OH)] \cdot H_2SO_4$ , m.p.  $117^\circ C.$  (132).

(e) *Action with a hydroxide.* Upon boiling an alcoholic solution of diphenylchloroarsine with alcoholic potassium hydroxide, diphenylarsenious oxide,  $(C_6H_5)_2As-O-As(C_6H_5)_2$ , m.p.  $89-91^\circ C.$  is formed (74, 75, 103); the melting point is also given as  $92.5-93.5^\circ C.$  (84).

(f) *Action with hydrogen peroxide.* The oxidation of diphenylchloroarsine is easily carried out with hydrogen peroxide at  $40-50^\circ C.$  and yields diphenylarsinic acid; probably  $(C_6H_5)_2As(OH)_2Cl$  occurs as an intermediate product,  $[(C_6H_5)_2As(OH)OAs(C_6H_5)_2(OH)_2]Cl$  being obtained when the oxidation is carried out in acetone with hydrogen peroxide (70).

(g) *Action with hydrogen and sodium sulfides.* Upon passing hydrogen sulfide into an alcoholic solution of diphenylchloroarsine, diphenylarsenious sulfide,  $(C_6H_5)_2As-S-As(C_6H_5)_2$ , separates as glistening white needles, m.p.  $64^\circ C.$  (72) or  $67^\circ C.$  It is readily soluble in benzene, carbon disulfide, chloroform, less soluble in alcohol, ether, and acetic acid, insoluble in alkalis and alkaline sulfides (90). When the chloroarsine is dissolved in benzene and shaken with a saturated solution of normal or acid sodium sulfide, diphenylarsenious sulfide is likewise formed (72, 84, 90, 96).

(h) *Action with thionyl chloride.* The interaction of diphenylchloroarsine and thionyl chloride on a water bath for ten minutes yields a definite crystalline, colorless addition compound of the composition,  $(C_6H_5)_2AsCl-$

$\text{SOCl}_2$  (47). Under reduced pressure this compound melts at 188–192°C. and begins to decompose at 195°C.; the distillate has the odor of chlorobenzene.

(i) *Action with nitrosyl chloride.* A benzene solution of diphenylchloroarsine on treatment with a benzene solution of nitrosyl chloride yields a white, crystalline precipitate of diphenyldichloroarsine oxide,  $[(\text{C}_6\text{H}_5)_2\text{AsCl}_2]_2\text{O}$ , m.p. 117°C. (111).

(j) *Action with sodium iodide.* Diphenyliodoarsine,  $(\text{C}_6\text{H}_5)_2\text{AsI}$ , is prepared by adding diphenylchloroarsine to an acetone solution of sodium iodide; yellow, hexagonal crystals, melting at 40.5°C., separate (133). The compound is insoluble in water, sparingly soluble in cold alcohol, readily soluble in hot alcohol, ether, acetone, benzene, carbon disulfide, and carbon tetrachloride.

(k) *Action with silver cyanide.* When diphenylchloroarsine is heated with an excess of dry silver cyanide, diphenylarsenious cyanide,  $(\text{C}_6\text{H}_5)_2\text{AsCN}$ , is formed. It crystallizes in colorless, monoclinic plates which have the odor of garlic and bitter almonds (103, 138, 139).

(l) *Action with sodium thiocyanate.* Diphenylthiocyanatoarsine,  $(\text{C}_6\text{H}_5)_2\text{AsCNS}$ , is formed by the reaction between acetone solutions of diphenylchloroarsine and sodium thiocyanate. It is a pale, brownish oil, boiling at 230–233°C. at 22–23 mm.; it is miscible with benzene and acetone in all proportions, but is decomposed by water (130).

(m) *Action with alkyl halides.* Diphenylchloroarsine when heated with methyl iodide in a sealed tube at 100°C. for three hours yields diphenyldimethylarsonium triiodide,  $(\text{C}_6\text{H}_5)_2\text{As}(\text{CH}_3)_2\text{I}_3$ . It crystallizes in violet needles, m.p. 69.5°C. It is insoluble in water and ether, but dissolves readily in hot alcohol, chloroform, ethyl acetate, and acetone (133).

Diphenylmethylarsine,  $(\text{C}_6\text{H}_5)_2\text{AsCH}_3$ , obtained when diphenylchloroarsine reacts with the ethereal solution of the Grignard reagent resulting from methyl bromide, boils at 156–157°C. at 11 mm. (134).

Diphenylethylarsine,  $(\text{C}_6\text{H}_5)_2\text{AsC}_2\text{H}_5$ , obtained when diphenylchloroarsine reacts with the ethereal solution of the Grignard reagent resulting from ethyl bromide, boils at 162–163°C. at 10 mm. (127).

Diphenylpropylarsine,  $(\text{C}_6\text{H}_5)_2\text{AsC}_3\text{H}_7$ , obtained when diphenylchloroarsine reacts with the ethereal solution of the Grignard reagent resulting from propyl bromide, boils at 177°C. at 10 mm.  $d_4^{20}$ , 1.1964. Its index of refraction at 20°C. is as follows:  $n_F = 1.6220$ ,  $n_D = 1.6054$ ,  $n_C = 1.5986$  (69).

Diphenylbutylarsine,  $(\text{C}_6\text{H}_5)_2\text{AsC}_4\text{H}_9$ , is obtained when diphenylchloroarsine reacts with the ethereal solution of the Grignard reagent resulting from butyl bromide; its boiling point has been given as 183°C. at 10 mm., and 197°C. at 17 mm. (69).

Diphenylisobutylarsine,  $(C_6H_5)_2AsCH_2CH(CH_3)_2$ , is obtained when the chloroarsine reacts with the ethereal solution of the Grignard reagent resulting from isobutyl bromide. It boils at  $185^\circ C.$  at 10 mm.;  $d_4^{20}$ , 1.1819 (69).

Diphenylamylarsine,  $(C_6H_5)_2AsC_5H_{11}$ , is obtained when diphenylchloroarsine reacts with the ethereal solution of the Grignard reagent resulting from amyl bromide. Boiling point,  $194^\circ C.$  at 10 mm.;  $d_4^{20}$ , 1.1617; index of refraction at  $20^\circ C.$ ,  $n_F = 1.5993$ ,  $n_D = 1.5846$ ,  $n_C = 1.5786$  (69).

Diphenyl-*dl*-amylarsine,  $(C_6H_5)_2As(dl)C_5H_{11}$ , is obtained when the chloroarsine reacts with the ethereal solution of the Grignard reagent resulting from *dl*-amyl bromide. Boiling point,  $195^\circ C.$  at 10 mm.;  $d_4^{20}$ , 1.1624 (69).

(n) *Action with zinc alkyls.* Diphenylmethylarsine,  $(C_6H_5)_2AsCH_3$ , prepared by the action of zinc methyl on diphenylchloroarsine (92), is a colorless, highly refractive oil, b.p.  $306^\circ C.$  or  $163\text{--}170^\circ C.$  at 15 mm., having a pungent, fruity odor. It is soluble in alcohol and benzene, and insoluble in water (20).

Diphenylethylarsine,  $(C_6H_5)_2AsC_2H_5$ , results when zinc ethyl reacts with the chloroarsine. It is a colorless liquid, b.p.  $320^\circ C.$ ,  $162\text{--}163^\circ C.$  at 10 mm. (74, 75, 92).

(o) *Action with sodium alcoholates.* The ethoxy compound,  $(C_6H_5)_2AsOC_2H_5$ , results when sodium ethoxide reacts with diphenylchloroarsine. It is a viscid oil, which partly solidifies when kept overnight (84).

Phenyldiphenylarsenite,  $(C_6H_5)_2As-OC_6H_5$ , is formed by treating a xylene solution of diphenylchloroarsine with sodium phenoxide. It is a colorless liquid, boiling at  $230\text{--}231^\circ C.$  at 15 mm.;  $d_4^{25}$ , 1.3113 (90).

Isoamyldiphenylarsenite,  $(C_6H_5)_2As-OCH_2CH_2CH(CH_3)_2$ , formed by treating a benzene solution of sodium isoamylate with diphenylchloroarsine in benzene, boils at  $188\text{--}189^\circ C.$  at 11 mm. It is pale green in color and has an odor resembling that of amyl alcohol (132).

Isoamyldiphenylthioarsenite,  $(C_6H_5)_2As-SCH_2CH_2CH(CH_3)_2$ , results on treatment of xylene solutions of diphenylchloroarsine with sodium isoamyl mercaptan. It is a greenish-yellow liquid, boiling at  $215\text{--}220^\circ C.$  at 11 mm. (132).

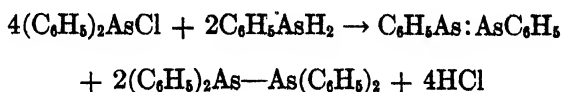
Allyldiphenylarsenite,  $(C_6H_5)_2As-OC_3H_5$ , is produced by treating a xylene solution of diphenylchloroarsine and sodium allylate. It is a pale green liquid, b.p.  $180.5\text{--}181.5^\circ C.$  at 11 mm. (132).

(p) *Action with phenylarsines.* When diphenylchloroarsine is mixed with phenylarsine in ether, hydrogen chloride is evolved and white needles of the triphenyldiarsine,  $(C_6H_5)_2As-AsH(C_6H_5)$ , separate. The reaction is carried out in an atmosphere of carbon dioxide (135).

Blicke and Powers (14), endeavoring to reproduce the work of Steinkopf

and Smie (135), were unable to obtain triphenyldiarsine, but obtained instead arsenobenzene and diphenylchloroarsine. Steinkopf and Smie merely analyzed their reaction product, which was not characterized by a melting point, and considered the arsenic analysis and the fact that a mixture of phenylarsinic and diphenylarsinic acids was obtained upon oxidation of their product with nitric acid sufficient proof for the claim that triphenyldiarsyl had been formed.

Tetraphenyldiarsine, phenylcacodyl,  $(C_6H_5)_2As-As(C_6H_5)_2$ , is obtained by the reaction of diphenylchloroarsine and diphenylarsine, dissolved in ether. It melts at 124–127°C. (14). It is also prepared when diphenylchloroarsine and phenylarsine are allowed to react in the ratio expressed in the following equation:



Besides tetraphenyldiarsyl there is likewise produced arsenobenzene, m.p. 210–211°C. (14).

Pentaphenyltriarsine,  $(C_6H_5)_2As-As(C_6H_5)-As(C_6H_5)_2$ . When phenylarsine and diphenylchloroarsine react in absolute alcohol in an atmosphere of carbon dioxide at 70°C., gas evolution soon takes place and a thick, white, crystalline mass of the triarsine separates (135).

(q) *Action with chloramine-T*. Diphenylarsinic acid is obtained by the interaction of chloramine-T on diphenylchloroarsine (21). The acid crystallizes in fine needles, 2 to 3 cm. long, m.p. 178°C., and showing a tendency to sublime at 192–200°C. (74, 89). It crystallizes from alcohol in short prisms and is somewhat soluble in ether and benzene; it is unattacked by boiling nitric or chromic acids.

(r) *Action with chloropicrin*. By treating the sodium salt (obtained as the result of the reaction of sodium ethoxide on diphenylchloroarsine) with chloropicrin, diphenylarsinic acid is prepared, m.p. 173–174°C. (149).

(s) *Action with turpentine and olive oil*. When diphenylchloroarsine is treated with turpentine which has been exposed to the air for some time and to rancid olive oil, it is oxidized to diphenylarsinic acid, m.p. 172°C. (145).

Walton and Eldridge (146) found that when chlorine is bubbled through diphenylchloroarsine the arsenic is oxidized to the pentavalent form and the resulting product is non-irritating when breathed by man and gave no reaction when titrated with iodine. Men gassed with diphenylchloroarsine were markedly benefited if given chlorine.



### *Test*

Fleury (40) devised an iodometric method whereby the amount of diphenylchloroarsine could be determined. Frahm and Boogaert (43) devised a method for the determination of diphenylchloroarsine, making use of the fact that diphenylchloroarsine can be saponified easily with sodium hydroxide solution and the resulting sodium chloride determined by the Volhard argentometric titration.

### *Physiological properties*

Diphenylchloroarsine strongly attacks the skin and is poisonous (92). A concentration of 0.000015 g. to 0.000025 g. per liter produces irritation of the nose and throat, while a concentration of 0.0005 g. per liter produces an intolerable atmosphere in 30 seconds (126, 144). Yet it requires between 0.001 to 0.002 g. per liter to cause the death of dogs after an exposure of thirty minutes (144). The highest concentration endurable for one minute is 1 to 2 mg. per cubic meter of particles  $10^{-4}$  to  $10^{-5}$  (3). Hanzlik and Tarr (64) found diphenylchloroarsine produced simple hyperemia without vesication, mild urticarial rash, moderate swelling and edema, and very little or no necrosis.

After a quick death by asphyxiation with diphenylchloroarsine, Manier and Morelli (85) found that the adrenals of guinea pigs showed an increase in adrenaline. In the vesicant action of diphenylchloroarsine the adrenaline decreases as the symptoms become worse, but this effect is short.

Diphenylchloroarsine has a special affinity for fats. This explains the damage to the liver and the resulting, defective fat metabolism. The poison is fixed in the circulating food fat, and carried with it to the liver, where it produces hepatitis. The excessive concentration of arsenic in the adrenals suggests that it has an affinity for fats other than the glycerides of the higher fatty acids. This affinity for fats may be due in some instances to the fat-solvent power of the poison, in others to the formation of oleates (42).

When one ear of a mouse was painted with 6 per cent solution of diphenylchloroarsine in petroleum ether, Berger and Groll (17) found that respiration ceased within eight hours.

### *Uses*

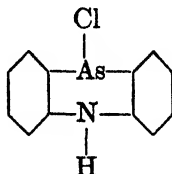
Tanner (140) found that pine piling treated with petroleum oil to which had been added diphenylchloroarsine showed pronounced resistance to marine borer attacks.

U. S. patent 1,565,237 was issued December 8, 1925 to Schmidt, Steindorff, Fluss, and Schaffrath (122) for treating seed grain for parasites; U. S. patent 1,652,291, December 13, 1927, to Tanner (142) for the use of an

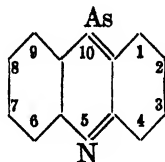
insecticide composed of diphenylchloroarsine; and U. S. patent 1,686,582, October 9, 1928, to Stoltzenberg (136) for the use of diphenylchloroarsine in destruction of cacti by action as vapor or spray or as injection of 5 per cent solutions in cresol or sulfuric acid.

V. DIPHENYLAMINECHLOROARSINE, PHENYLARSAZINE CHLORIDE, 10-CHLORO-5,10-DIHYDROPHENARSAZINE,  $\text{NH}(\text{C}_6\text{H}_4)_2\text{AsCl}$

The reaction between arsenious halides and secondary aromatic amines was the subject of German patent 281,049 of F. Bayer and Company in 1913 (11). Wieland and Rheinheimer (148) made a comprehensive study of the derivatives of the compound obtained by condensing arsenious chloride and diphenylamine. To this compound Wieland and Rheinheimer gave the name phenarsazine chloride and ascribed to it the constitution



which is the same as that assigned to it by the patentees. Wieland and Rheinheimer prepared the compound phenarsazine, which undoubtedly has the structure



The product of the reaction between diphenylamine and arsenious chloride is the same as that derived from phenarsazine by the addition of hydrochloric acid. This compound has heretofore been variously known as diphenylaminearsenious chloride (29, 30) and 6-chlorophenarsazine (78, 79). In systematically describing this class of compounds, the name "phenarsazine" is retained for the parent substance and the atoms numbered as indicated. The products of the reaction between diphenylamine and arsenious chloride and its simple derivatives are regarded as substitution products of 5,10-dihydrophenarsazine.

Although the patent referred to was taken out in 1913 and issued in the German Empire in December 1914, the specification was not available elsewhere until September 1920. Burton and Gibson (22) had but a re-

stricted knowledge of this type of heterocyclic compound up to 1918, limited to that contained in a brief abstract of the patent, which referred only to the general reaction between arsenious chloride and diarylamines without mentioning any specific compound. Ball independently prepared the compound early in 1918 (unpublished report) by the action of arsenious chloride on diphenylamine and examined a number of its simpler derivatives. G. T. Morgan in 1918 (unpublished report) also studied the reaction and prepared certain analogues of 10-chloro-5,10-dihydrophenarsazine. The bulk of the investigations on this compound and its derivatives of recent years has been carried out by Gibson and his coworkers (22, 23, 24, 25, 46, 48).

### *Preparation*

Diphenylaminechloroarsine is prepared: (a) when diphenylamine or methyldiphenylamine, arsenious chloride, and *o*-dichlorobenzene are boiled under a reflux for five hours (22, 144, 148); (b) when diphenylhydrazine is heated with arsenic trichloride (78); (c) when 2-bromo-6'-methylaminodiphenylarsinic acid, dry potassium carbonate, amyl alcohol, and a trace of powdered copper are boiled under a reflux for twelve hours (22, 148); (d) by condensation of phenyldichloroarsine with diphenylamine in *o*-dichlorobenzene solution (the presence of the solvent is not essential) (23, 58); (e) by condensation of  $\beta$ -chlorovinylchloroarsine and diphenylamine with or without a solvent (23, 120); (f) by reducing diphenylamine-*o*-arsinic acid or phenarsazinic acid in hot alcohol-hydrochloric acid solution with sulfur dioxide, after adding a trace of iodine (46); (g) upon heating a perchloride of 10-methyl- or 10-phenyl-5,10-dihydrophenarsazine (123); (h) by treating fused diphenylamine with concentrated hydrochloric acid (density 1.08), heating and stirring until almost free from water, and then mixing with arsenious oxide and fusing for four hours (29); (i) by boiling aniline and arsenic trichloride for seventy-two hours, adding sodium hydroxide, and steam distilling; the crude oxy compound is then treated with hydrochloric acid and acetone (22); (j) upon boiling a mixture of 10,10'-oxy-5,10-dihydrophenarsazine, benzoyl chloride, and dry benzene under a reflux for six hours (22); (k) by condensation of (1) phenyl-*p*-tolylamine, (2) *p,p'*-ditolylamine, or (3) phenyl- $\alpha$ -naphthylamine with dichloroarsine and *o*-dichlorobenzene by boiling for sixteen hours (23); (l) by heating trianilinearsine hydrochloride (121).

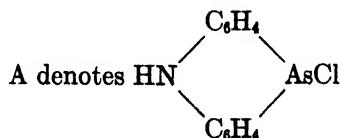
### *Physical properties*

Diphenylaminechloroarsine crystallizes from carbon tetrachloride, ether, benzene, or xylene in yellow needles, melting at 186–187°C. (22), 187–190°C. (22), 189–190°C. (23), 190–191°C. (22), 191°C. (46), 191–192°C.

(22), 191–193°C. (105), 192–193°C. (78, 148), 192.5°C. (141), 193°C. (79, 148), 193–194°C. (126), 195°C. (3, 137, 144, 146). Fischer (39) found the chloroarsine to crystallize in three forms: the stable modification is orthorhombic and melts at 195°C.; of the metastable crystals, some are monoclinic and melt at 186°C. whereas others are triclinic melting at 182°C. The crystals sublime *in vacuo* (78, 148). The compound boils at 120–121°C. at 9–10 mm. (120), and at 410°C. with decomposition (3, 137, 144, 146).  $d_{40}^{20}$ , 1.6766 (120). Specific heat, 0.268 (126). It is soluble in concentrated sulfuric acid forming a dark red solution, but on addition of water the orange-yellow sulfate precipitates (58). Its heat of vaporization has been calculated as 54.8 calories per gram. Its vapor pressure is practically negligible at all temperatures, being only  $5 \times 10^{-16}$  mm. at 0°C. and  $2 \times 10^{-6}$  mm. at 100°C. (126). A saturated concentration at 20°C. contains 0.02 mg. per cubic meter. (3). Its fumes are inflammable (126).

One of the most striking properties of phenylarsazine hydrochloride is its power of forming molecular compounds. When the phenarsazine is crystallized from the following solvents the crystals effloresce slowly in the air, but heating to 110°C. causes rapid dissociation, leaving the pure phenarsazine in each case:

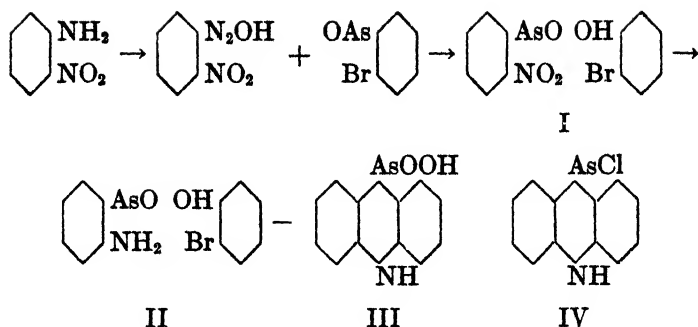
(a) acetic acid	$A \cdot C_2H_4O_2$
(b) <i>s</i> -tetrachloroethane	$2A \cdot C_2H_2Cl_4$
(c) chlorobenzene	$2A \cdot C_6H_5Cl$
(d) <i>o</i> -dichlorobenzene	$2A \cdot C_6H_4Cl_2$
(e) acetone	$2A \cdot C_3H_6O$
(f) carbon tetrachloride	$A \cdot CCl_4$



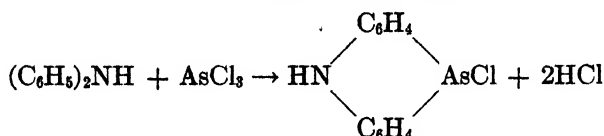
10-Chloro-5,10-dihydrophenarsazine is extremely soluble in arsenic trichloride, giving a dark green solution. A hot, concentrated solution on cooling deposits magnificent, scarlet scales of the compound  $A \cdot AsCl_3$ . This is sufficiently stable to permit filtration, but on exposure to air or washing with solvents yields the original chloro compound (22).

### Constitution

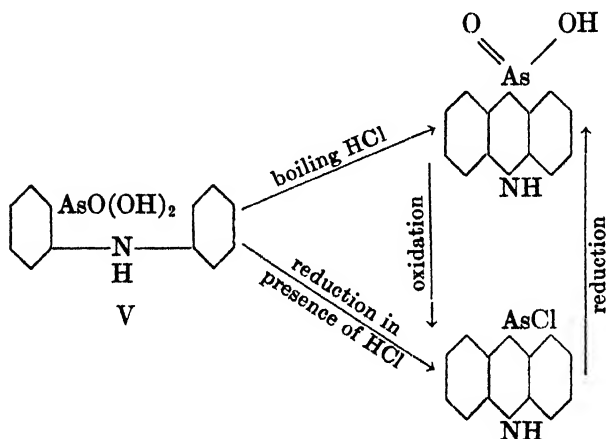
The constitution ascribed to 10-chloro-5,10-dihydrophenarsazine has been proved to be correct by the following synthesis, which may be represented diagrammatically:



Diazotized *o*-nitroaniline coupled with *o*-bromophenylarsenious oxide yields 2-bromo-6'-nitrodiphenylarsinic acid (I), reduction of which by ferrous hydroxide gives the corresponding amino derivative (II), which, when heated in amyl alcohol with potassium carbonate and a small quantity of copper powder, is readily converted into phenarsazinic acid (III); this substance, when reduced in hydrochloric acid-ethyl alcohol solution by sulfur dioxide, is converted into 10-chloro-5,10-dihydrophenarsazine (IV), identical with the substance prepared by the action of arsenious chloride on diphenylamine according to the equation:



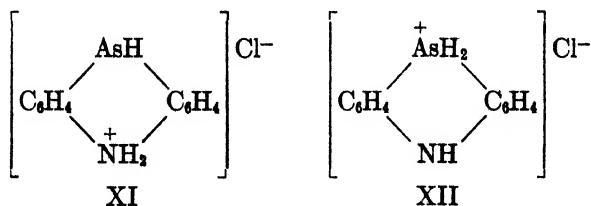
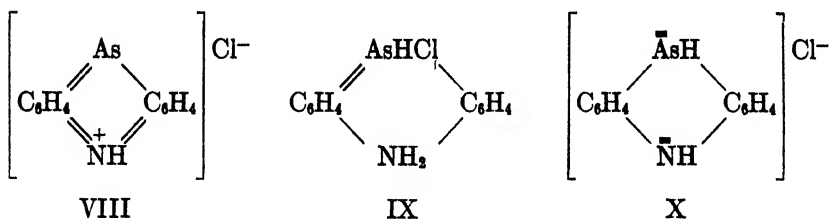
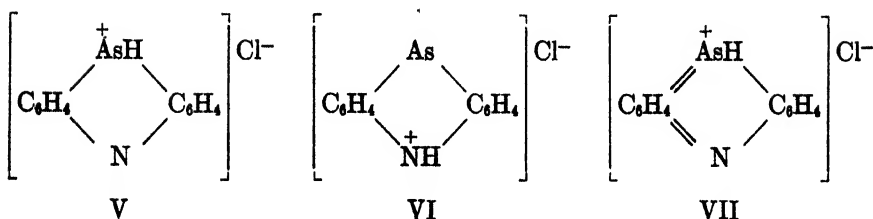
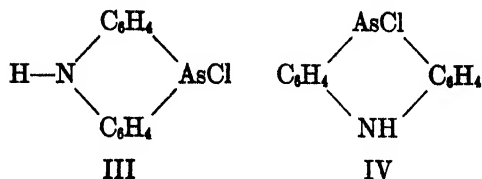
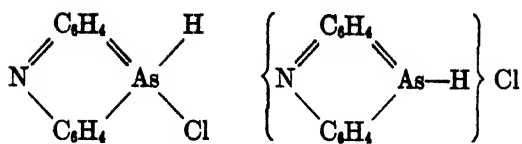
The presence of the :NH group is shown by the fact that the hydrogen may be replaced by acetyl or similar groups. A further verification of the structure is offered by the following series of reactions:



Diphenylamine-*o*-arsinic acid (V), prepared by the condensation of *o*-bromophenylarsinic acid and aniline, when reduced in alcohol-hydrochloric acid solution by sulfur dioxide in the presence of iodine, gives 10-chloro-5, 10-dihydrophenarsazine, or, if boiled with concentrated hydrochloric acid, yields the chloride of phenarsazinic acid, which may be reduced to the 10-chloro compound under suitable conditions (46).

Kappelmeier (70) has expressed the view that the constitution of 10-chloro-5, 10-dihydrophenarsazine is more adequately expressed by formula I or II than by III (50). The first formal proof that the substance possesses formula III was given by Gibson and Burton (22), who also showed that the original method of preparation of these phenarsazine derivatives was strictly limited and could not be applied even to the nitro and carboxyl compounds (25, 46). As to the existence of the *N*-methyl derivatives which Wieland and Rheinheimer (148) claimed to have obtained in small quantity by the condensation of diphenylmethylamine with arsenic trichloride, Gibson and coworkers were only able to isolate from this reaction a small quantity of the phenarsazine (22, 49, 51); the desired synthesis was also unsuccessful as was also the methylation of the parent compound. Gibson, Johnson, and Vining (50) had already shown that the constitution of the phenarsazine may be represented by the formulas IV, V, VI, VII, or VIII, the compound being probably best represented by V or VI, which might be in equilibrium, although no definite proof could be advanced in favor of the transannular band formulas as against the *o*-quinoid formulas. Whereas all tervalent arsenic derivatives in this series are colored except the *N*-acetyl derivatives, the quinquivalent arsenic derivatives are colorless, unless a chromophoric group is present. Having adopted the transannular band for 10-chloro-5, 10-dihydrophenarsazine, it seemed clear that the color of this substance must be associated with the presence of this band, since those derivatives are colorless. It was therefore necessary that two types of derivatives be assumed, those without the transannular band (the "true dihydrophenarsazines" according to Kappelmeier), and those with the transannular band, which are salts. The structure IV may be preserved by acetylation of the hydrogen atom of the :NH group, or this hydrogen atom may be bound to the nitrogen by its forming part of the chelate ring, provided a suitable group is present, as, e.g., the nitro group in the 4-position. If 10-chloro-5, 10-dihydrophenarsazine does not contain the :NH group it must be capable of reacting in this form, since the *N*-acetyl derivatives are so readily formed by the residual reactions. From formulas V and VI and from formulas VII and VIII the former are to be preferred, since arsenic displays a remarkable tendency to pass into the "onium" condition; then the 10-chloro compound must have a formula which allows the free migration of the hydrogen atoms from  $N \rightleftharpoons As$ . If

the nitrogen and arsenic are intimately connected, this wandering will be facilitated and this is an important reason for the adoption of the transannular band formula. On preparing 10-chloro-5,10-dihydrophenarsazines from substituted diphenylamines and arsenic trichloride the formation of an addition compound is often observed (changes of color and evolution of heat on simple mixing). It was now found that the following compounds condense: diphenylamine, *o*-, *m*-, and *p*-phenyltolylamines, 2,3'-, 2,4'-, and 4,4'-ditolylamines,  $\alpha$ - and  $\beta$ -naphthylphenylamines, *m*- and *p*-phenylchlorobenzeneamines, 4,4'-, 3,4-, and 3,5-dichlorodiphenylamines, *p*-diphenylbenzidine,  $\alpha$ - and  $\beta$ -dinaphthylamine, *p*-tolyl- $\alpha$ - and *p*-tolyl- $\beta$ -naphthylamine, *m*- and *p*-phenylanilineamine, *N,N'*-di-*p*-tolylhydrazine, *m*- and *p*-dianilinebenzene, and *p*-diphenylhydroxylamine. No condensation was obtained with diphenylmethylaniline, *o*-phenylanilineamine, *o*-, *m*-, and *p*-phenylnitrophenylamines, 4,4'- or 2,4-diaminodiphenylamine-, *p*-dinitrophenylamine, *o*-chlorodiphenylamine, 2,4- and 2,5-dichlorophenylphenylamine, 2,4-dichlorodiphenylamine, 2,4-dibromodiphenylamine, diphenylacetylaniline, diphenylformylaniline, diphenylbenzoylamine, *o*-diphenylaminebenzene, and dicyclohexylamine. The halodiphenylamines fall into two classes, those with at least one halogen atom in the *o*-position to the :NH group, which do not condense, and those which do not have the halogen atom in this position and which do condense with arsenic trichloride. Nitro derivatives as a rule do not condense, and the compounds which do not react all possess alkyl or phenylene substituting groups; the absence of a reaction is sometimes to be ascribed to steric hindrance. The red color of the solution obtained by Wieland and Rheinheimer by the reduction of 10-chloro-5,10-dihydrophenarsazine with zinc in acetic acid disappeared on further reduction and reappeared on addition of the starting product; it was therefore suggested that the completely reduced solution contains the compound IX, while the colored solution contains the quinhydrone substance (IV and IX). Razuvaev (105, 106, 107, 108), however, considers these colored compounds to be of the meriquinonoid type X. The existence of such a compound having an odd number of valence electrons in the molecule must, for the present, be considered doubtful. Neither is the formula IX in accordance with modern views on quinquevalent nitrogen, and it is suggested that the formula of the completely reduced substance should be represented by XI or XII, the absence of the color being due to the absence of the transannular band. Attempts to condense 10-chloro-5,10-dihydrophenarsazine with methyl-ethylmalonate were unsuccessful, diphenylarsinic acid being obtained. The action of hydrogen chloride on 10-chloro-5,10-dihydrophenarsazine at high temperatures gives appreciable quantities of arsenic trichloride and diphenylarsine.



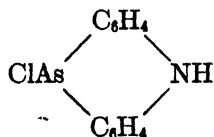
Previous work in this series has shown that condensation between arsenious chloride and substituted diphenylamines ordinarily produces 5,10-dihydrophenarsazine derivatives, but Elson and Gibson (36) have shown that it does not take place: (i) when at least one nitro group is present, as in *o*-nitro, *m*-nitro, 4,4'-dinitro-, and 2,4-dinitrodiphenylamines; (ii) when an amino group occupies one ortho position as in *o*-aminodiphenylamine; (iii) when two amino groups are present, e.g., the cases of 2,4-diamino- and



4,4'-diaminodiphenylamines; (iv) when an alkyl or acyl group is substituted for the hydrogen in the :NH group, e.g., *N*-methyl, *N*-formyl, *N*-acetyl-, and *N*-benzoyldiphenylamines; (v) when the benzene nuclei are fully reduced, e.g., dicyclohexylamine; (vi) in the unique case of *N,N'*-diphenyl-*o*-phenylenediamine, the corresponding *m*-phenylene and *p*-phenylene compounds readily undergoing condensation.

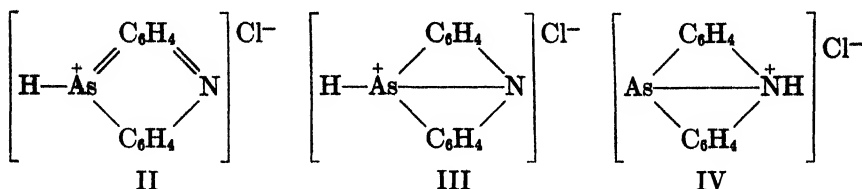
The last failure may be due to steric hindrance: cases (ii), (iii), and (v) may be explained by the stability of the addition compounds of arsenic trichloride and highly basic diphenylamine derivatives, for the initial formation of which, in the reaction, evidence has been brought forward (22, 55), and (iv) may be due to the hydrogen of the :NH group playing an essential part in the changes leading to the final condensation product. As regards case (i) it may be that the nitro group reduces the basicity of diphenylamine to such an extent that the initial compound formation mentioned above does not take place at all.

Kappelmeier previously showed (70) that the formulation of the reaction product of arsenic trichloride and diphenylamine as 10-chloro-5,10-dihydrophenarsazine,



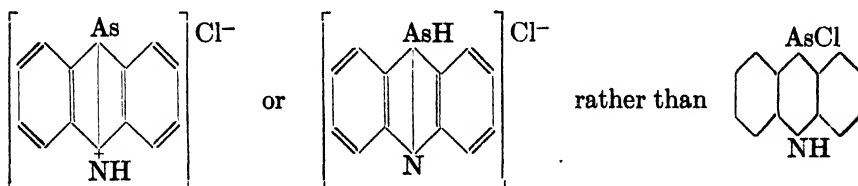
(formula I) is not in accordance with the salt-like properties and color of this substance; formula II, which gives an adequate account of these properties, was therefore preferred. Gibson and Johnson (55), however, prefer a formulation as a salt, but with a bridge between the arsenic and nitrogen atoms (III and IV), and it is now pointed out (71) that a decision on this point cannot be obtained from the synthesis, the sudden formation of a colored compound at the end of the reaction pointing to an intermolecular change. Kappelmeier does not agree with Gibson and Johnson either on the question whether the color is to be ascribed to a tervalent or to a quinquevalent arsenic atom; whereas Gibson and Johnson ascribe the color to the tervalent arsenic atom, Kappelmeier holds the opinion that tervalent as well as quinquevalent arsenic compounds may be colored or colorless, examples of both cases being known. The easy formation of a colorless *N*-acyl derivative, which, according to Gibson and Johnson, points to the existence or easy formation of an :NH group, is explained by Kappelmeier by primary addition to the nitrogen atom followed by splitting off of hydrogen chloride. The *o*-quinonoid formulation is preferred by Kappelmeier in view of the greater reactivity of the compound as compared with 10-

chloro-5,10-dihydrophenarsazine; moreover, in analogous compounds such as anthracene and acridine, the *o*-quinonoid formulation (7, 8) has been preferred in recent years to the bridged formula.



Gibson, Hiscocks, Johnson, and Jones (45) found the colors of 10-chloro-5,10-dihydrophenarsazine and of its methyl, nitro, and nitromethyl derivatives to be very intense. The parent substance and its methyl derivatives in the solid state have a brilliant yellow color, but the colors of the nitro derivatives depend on the position occupied by the nitro group. The previous knowledge of the visible color and known constitution of some of the latter compounds indicate that those possessing a deep crimson color have the nitro group in the 1- or 4- position, whereas those which are yellow have the nitro group in the 2- or 3-position in the phenarsazine nucleus. Although the exact relationships between chemical constitution and the absorption spectra of substances in solution are far from being understood, it is shown in the present discussion that in the series of closely related compounds the absorption spectra can be correlated with the position of the nitro group in the nucleus.

Evidence has been brought forward by Gibson and Johnson (50) to indicate that the constitution of 10-chloro-5,10-dihydrophenarsazine is more adequately represented either by

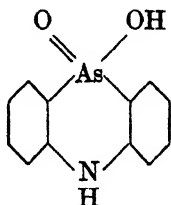


since apart from other properties, the *N*-substituted derivatives are colorless and they cannot possess a transannular band.

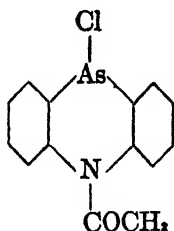
All the simple derivatives of 10-chloro-5,10-dihydrophenarsazine in which the arsenic atom is in the trivalent condition are yellow unless the hydrogen of the :NH group has been replaced by an acyl group, in which case the compounds are practically colorless (1, 123).

Wieland and Rheinheimer (148) suggested that the yellow color of 10-

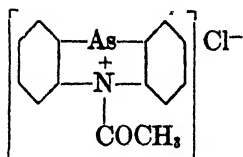
chloro-5,10-dihydrophenarsazine was due to an atomic intervention between the arsenic and nitrogen atoms which involves their possessing a quinonoid-like structure. Sufficient experimental evidence has now been proved to ascribe to this parent compound the constitution 1 or 2, which may be in equilibrium. Since visible color is absent in the case of phenarsazinic acid,



where a transannular N—As band is precluded, it would appear that the yellow color of 10-chloro-5,10-dihydrophenarsazine is due to the presence of the transannular structure indicated above. The colorless nature of 5-acetyl-10-chloro-5,10-dihydrophenarsazine,



is readily explained, since the presence of a transannular band as in



would necessitate the nitrogen atom carrying a positive charge although it has the negative acetyl group attached to it.

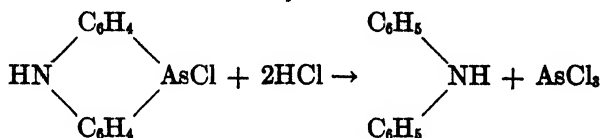
Gibson, Hiscocks, Johnson, and Jones (45) were of the opinion that it was reasonable to assume that any absorption in the visible and near ultraviolet spectrum of the parent substance may be associated with this transannular band. They found a strong absorption band in the near ultraviolet, the center of the band being at the frequency of  $8.65 \times 10^{14}$ , while marked absorption occurred in the extreme violet. A strong double

branched absorption band occurs further in the ultra-violet, with two maxima at frequencies of  $10.0 \times 10^{14}$  and  $10.8 \times 10^{14}$ .

A Hilger C-type quartz spectrograph and a Hilger sector photometer were used, with an iron-nickel arc as a source of radiation. A concentration of  $M/10,000$  in optically pure ethyl alcohol gave the best results in the ultra-violet region for 1-cm. length of tube, but in certain cases it was necessary to supplement the results so obtained by using a concentration of  $M/4000$  in order to follow the absorption band more fully.

### Chemical properties

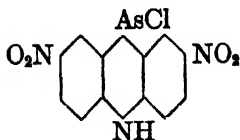
(a) *Action with acids.* When diphenylaminechloroarsine is heated with hydrochloric acid it is decomposed into diphenylamine and arsenic trichloride (55, 112, 123):



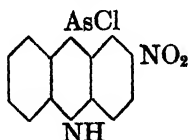
10,10'-Bis-5,10-dihydrophenarsazine,  $[\text{HN}(\text{C}_6\text{H}_4)_2\text{As}]_2$ , is prepared by treating a hot mixture of phenarsazine chloride in alcohol-acetone solution with hypophosphorous acid (density 1.136); on cooling the orange-yellow needles separate, m.p.  $304-305^\circ\text{C}$ . with decomposition. It is very sparingly soluble in the usual organic solvents. It is moderately stable under ordinary conditions, but when boiled with xylene or acetone it is rapidly oxidized, producing the colorless phenarsazinic acid (24).

Razuvaev, Godina, and Yemelyanova (111) found that the action of nitrous acid on 10-chloro-5,10-dihydrophenarsazine does not yield the expected nitroso derivative.

Wieland and Rheinheimer (148) found that when phenarsazine chloride was nitrated it led to the production of two mononitro compounds and a dinitro derivative. The chloride is dissolved in boiling acetic acid, the solution rapidly cooled to  $18^\circ\text{C}$ . and nitric acid (density 1.52) added dropwise, the temperature being maintained below  $20^\circ\text{C}$ . Each drop of acid produces a blue coloration, and when all has been added the temperature is raised to  $25^\circ\text{C}$ . when complete solution takes place; on subsequent cooling a deep-colored dinitro compound separates. The two mononitro derivatives are dissolved in cold acetone, the *p,p'*-dinitrophenarsazine chloride



remains undissolved. It forms pale yellow needles, melting above 300°C. Upon evaporating the acetone solution from the dinitro compound and extracting with benzene, the *p*-derivative,

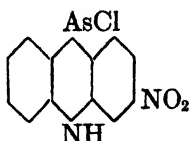


dark, greenish-yellow leaflets, remains practically insoluble; on heating it turns dark red at about 194–197°C. and melts at 276–278°C. with decomposition (46). The *o*-nitrophenarsazine chloride,

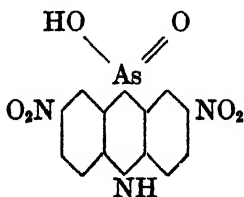


the benzene residue, is then dissolved in ether and finally crystallized from benzene and acetic acid as scarlet-red needles, m.p. 156°C. (148) or 165°C. (46).

Gibson and Johnson (54) prepared 10-chloro-3-nitro-5,10-dihydrophenarsazine,

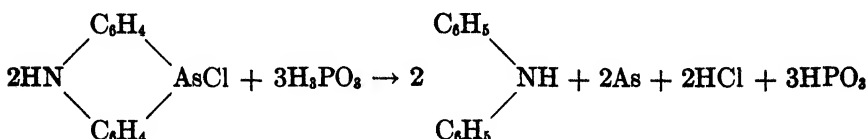


as orange-colored needles, decomposing at 268–271°C. Razuvaev and Koton (113) found that upon mild nitration of diphenylaminechloroarsine, diphenylenearsinic acid,  $[(C_6H_5)_2As(OH)_2]NO_3$ , is produced; a more energetic nitration results in the formation of *m*-dinitro acids. When phenarsazine chloride is added to warm concentrated nitric acid (density 1.4) and the solution raised to the boiling point 2,8-dinitrophenarsazinic acid is obtained.

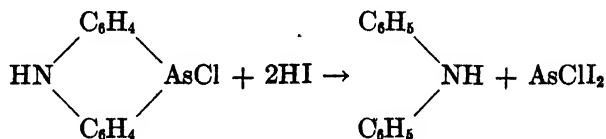


It crystallizes from nitrobenzene in pale yellow needles melting above 300°C. (148).

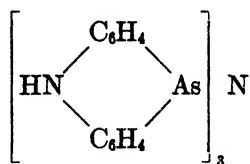
Upon heating diphenylaminechloroarsine to 120–180°C. with phosphorous acid, elementary arsenic is split off (109):



Upon treating 10-chloro-5,10-dihydrophenarsazine with hydriodic acid, the phenarsazine is decomposed (109):

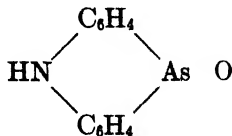


(b) *Action with alkali.* When ammonia is passed into a solution of phenarsazine chloride in dry boiling xylene, a colorless, chlorine-free body is obtained, which appears to be triphenarsazine amine,



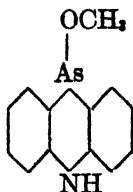
a sparingly soluble, white precipitate which melts with decomposition at 295–300°C. (148).

Phenarsazine oxide, 10,10'-oxy-5,10-dihydrophenarsazine,



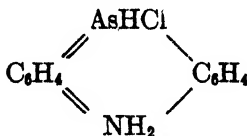
is produced by the action of alkali upon an acetone solution of phenarsazine chloride. It crystallizes from nitrobenzene or pyridine in colorless plates, which soon become yellow, m.p. 350°C. It is sparingly soluble in most solvents, and when boiled with alcohols yields ethers; with phenols, it yields phenyl ethers (148).

## Phenarsazine methyl ether,



is prepared by treating a methyl alcohol suspension of phenarsazine chloride with sodium methylate. The ether crystallizes in long, colorless needles, melting at 194°C. to a yellow liquid (148). Upon boiling with alkali or water, it gives the oxide, which, when boiled with methyl alcohol, again gives the methyl ether.

(c) *Action with a metal.* 10-Chloro-5,10-dihydrophenarsazine is quantitatively reduced by the action of zinc dust and acetic acid in an inert atmosphere to 5,10-dihydrophenarsazine hydrochloride (110).

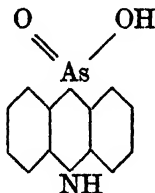


(d) *Effect of heat.* By heating dihydrophenarsazine chloride in tetrahydronaphthalene in the presence of oxygen or a trace of water, phenarsazinic acid is produced (124).

The hydrochloride of phenarsazinic acid is obtained by heating 10-chloro-5,10-dihydrophenarsazine for thirty minutes at 100–120°C. in an oil bath; it crystallizes from absolute alcohol, and melts at 207–208°C. (124).

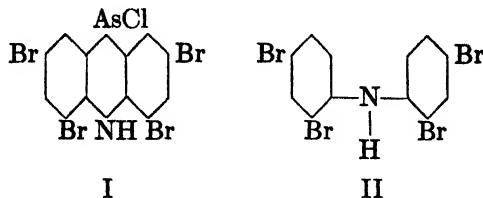
(e) *Action of hydrogen peroxide.* Phenarsazinic acid, prepared by suspending phenarsazinic chloride in acetic acid and adding a small excess of hydrogen peroxide and warming, is obtained as felt-like needles, m.p. above 300°C. (148).

(f) *Action of halogens.* Phenarsazinic acid,

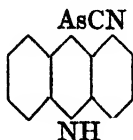


is prepared by treating phenarsazine chloride in water solution with iodine (114). On treating a hot glacial acetic acid solution of 10-chloro-5,10-

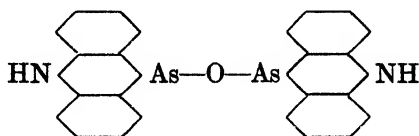
dihydrophenarsazine with bromine a colorless, well-defined crystalline substance is isolated from the cooled solution. It was expected that the fully brominated product would be 10-chloro-2,4,6,8-tetrabromo-5,10-dihydrophenarsazine (I), but the colorless product isolated was arsenic-free and analysis showed it to be tetrabromodiphenylamine (II), m.p. 186°C. (37).



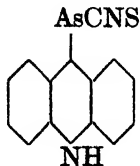
(g) *Action with silver cyanide.* 10-Cyano-5,10-dihydrophenarsazine



is obtained from the corresponding 10-chloro compound and silver cyanide in benzene solution. It melts with decomposition at 227–228°C. (62) or 223–224°C. (55). On hydrolysis, it forms the compound (62)



(h) *Action with potassium thiocyanate.* 10-Thiocyano-5,10-dihydrophenarsazine,



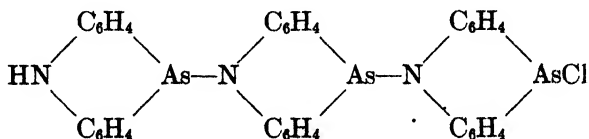
is obtained by treating 10-chloro-5,10-dihydrophenarsazine in acetone with a water solution of potassium thiocyanate on a water-bath; it crystallizes in yellow crystals from *o*-dichlorobenzene, and from carbon tetrachloride in red needles. Its melting point is given as 229–230°C. (124) or 238–240°C. (decomposition) (55). The yellow crystals with neutral solvents



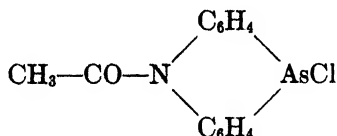
(xylene, toluene, chloroform, phenyl bromide, etc.) are transformed on boiling into a mixture of yellow needles and dark red plates, and on prolonged standing at room temperature into red plates, which, in turn, are converted back into the yellow form by recrystallization from solvents having an oxygen atom in their molecule. The mixture of the two forms causes no depression of the melting point (124).

(i) *Action with chloramine-T.* By treating a cold alcoholic solution of 10-chloro-5,10-dihydrophenarsazine with chloramine-T, phenarsazinic acid is prepared (21).

(j) *Action with pyridine.* On boiling phenarsazine chloride in dry pyridine for two hours, an orange-yellow, crystalline product is formed, triphenarsazine chloride, melting at 260–263°C. Its properties and analysis point to the following structure (148).

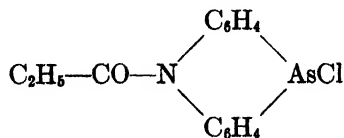


(k) *Action with acetyl chloride.* 10-Chloro-5-acetyl-5,10-dihydrophenarsazine,



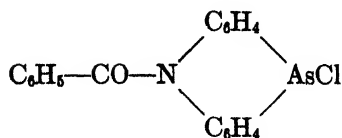
is prepared by boiling an excess of acetyl chloride, diluted with dry benzene, with 10-chloro-5,10-dihydrophenarsazine for four hours. The substance crystallizes on cooling and is obtained in small, colorless needles, m.p. 229–230°C. (21).

(l) *Action with propionic anhydride.* 10-Chloro-5-propionyl-5,10-dihydrophenarsazine,



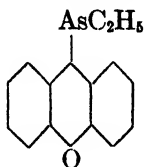
is prepared by boiling 10-chloro-5,10-dihydrophenarsazine with a large excess of propionic anhydride, and a small amount of pyridine, diluted with dry xylene, for ten hours. It crystallizes as colorless plates, melting at 135–136°C. (21).

(m) *Action with benzoyl chloride.* 10-Chloro-5-benzoyl-5,10-dihydrophenarsazine,



is prepared by boiling 10-chloro-5,10-dihydrophenarsazine in an excess of benzoyl chloride, diluted with dry xylene, for ten hours. After removal of excess xylene the dark colored viscous oil is allowed to stand for two days and the solid material filtered off; it is obtained as colorless crystals, m.p. 180–181°C. (21).

(n) *Action with ethyl bromide.* 10-Ethylphenoxarsine,



is obtained upon adding a warm benzene solution of phenarsazine chloride to the Grignard reagent prepared from ethyl bromide and magnesium; it boils at 194°C. at 20 mm. (2).

Aeschlimann (1) found that 10-chloro-5,10-dihydrophenarsazine reacts with two molecules of the respective Grignard reagents to give 10-methyl-, 10-ethyl-, and 10-phenyl-5,10-dihydrophenarsazine, hydrocarbons also being formed owing to the presence of the :NH group. When the reaction mixture is cooled during the addition of 10-chloro-5,10-dihydrophenarsazine, the formation of hydrocarbon does not take place and the heavy oil which separates from the ethereal solution should contain the :NH(MgI)R group. Treatment of this with methyl iodide, however, does not produce 5,10-dimethyl-5,10-dihydrophenarsazine, but 10,10-dimethyl-5,10-dihydrophenoxarsonium iodide, which is also the product when the methylation of 10-methyl-5,10-dihydrophenarsazine is attempted under various conditions. The latter compound, unlike 10-chloro-5,10-dihydrophenarsazine (148), which loses hydrogen chloride from the 5,10-position to produce phenarsazine when heated in a vacuum, loses methyl iodide under these conditions and re-forms 10-methyl-5,10-dihydrophenarsazine.

10-Methyl-, 10-ethyl-, 10-propyl-, 10-isopropyl-, 10-butyl-, 10-isobutyl-, 10-sec-butyl-, 10-amyl-, and 10-diethylmethyl-5,10-dihydrophenarsazines have been prepared by the action of the appropriate alkylmagnesium halide on 10-chloro-5,10-dihydrophenarsazine (1). These are all highly

crystalline compounds whose lack of color is explained by the theory of color of dihydrophenarsazines previously elaborated (50, 55). These compounds have a mildly irritating effect on the skin of the face and are readily decomposed by treatment at 110–130°C. with dry hydrogen chloride.

In table 4 are given the densities (reduced to vacuum standard) and the boiling points under various pressures of the above eight dichloroalkylarsines. From the slope of the boiling point–pressure curves (which are not quite accurately represented by an equation of the form  $A - \log_e p = K/T$ ), the molecular heats of vaporization and Trouton's constant at 760 mm. are calculated to be:  $\text{MeAsCl}_2$ , 7890 calories, and 19.4;  $\text{C}_2\text{H}_5\text{AsCl}_2$ , 9180 calories, and 21.4;  $\text{C}_3\text{H}_7\text{AsCl}_2$ , 10,400 calories, and 23.1; *iso*- $\text{C}_3\text{H}_7\text{AsCl}_2$ ,

TABLE 4  
Densities and boiling points of the dichloroalkylarsines

SUBSTANCE	$d_{40}^{20}$ VACUUM	MELTING POINT  °C	BOILING POINT AT					
			20 mm	50 mm.	100 mm	200 mm.	400 mm	760 mm
			°C.	°C.	°C.	°C.	°C.	°C.
$\text{MeAsCl}_2$ .....	1.8358	–42.5		55.5	72.1	89.1	109.1	132.5
$\text{EtAsCl}_2$ .....	1.6595			74.0	90.0	109.6	131.2	155.3
$\text{PrAsCl}_2$ .....	1.5380	–28.2		88.8	107.5	126.9	151.2	175.3
<i>iso</i> - $\text{PrAsCl}_2$ .....	1.4900		67.0	85.5	102.6	121.0	145.0	168.6
$\text{BuAsCl}_2$ .....	1.4664		90.5	105.0	125.6	147.2	172.0	194.1
<i>iso</i> - $\text{BuAsCl}_2$ .....	1.4465		77.8	95.8				
<i>sec</i> - $\text{BuAsCl}_2$ .....	1.4128		85.0	99.4	113.7	132.1	156.7	181.3
$\text{AmAsCl}_2$ .....	1.4035	–45.5	103.0	123.1	142.6	164.1	189.0	212.9

11,500 calories, and 26.0;  $\text{C}_4\text{H}_9\text{AsCl}_2$ , 12,200 calories, and 26.2; *sec*- $\text{C}_4\text{H}_9\text{AsCl}_2$ , 10,700 calories, and 23.5;  $\text{C}_6\text{H}_{11}\text{AsCl}_2$ , 11,950 calories, and 24.6, respectively. The somewhat high values in some cases of Trouton's constant may indicate some association in the liquid state. If the densities of the *n*-alkyl-dichloroarsines are plotted against the number of carbon atoms, an anomaly is revealed in the case of the butyl compound.

The following 10-alkyl-5,10-dihydrophenarsazines have been prepared: 10-methyl-, m.p. 105°C. (1), 106–107°C. (53), 107–108°C. (123); 10-ethyl-, m.p. 71–72°C. (123), 75°C. (1, 126), 10-propyl-, m.p. 81–82°C. (114), 85.5–86.5°C. (53); 10-isopropyl-, m.p. 87–88°C. (53); 10-butyl-, m.p. 94–95°C. (53); 10-isobutyl-, m.p., 73–74°C. (53); 10-*sec*-butyl-, m.p. 85–86°C. (53); 10-amyl-, m.p. 90–92°C. (53); 10-isoamyl-, m.p. 76–78°C. (114); 10-diethylmethyl-, m.p. 110–111°C. (53); 10-phenyl-, m.p. 142°C. (1), 148–149°C. (114, 123); 10- $\alpha$ -naphthyl-, m.p. 154–155°C. (123).

In concentrated sulfuric acid, all the alkyl derivatives yield deep red

solutions; those of the ethyl, isopropyl, *sec*-butyl, and diethylmethyl compounds become green on addition of a little concentrated nitric acid; in all cases the color changes to brown or reddish-brown with excess concentrated nitric acid. They all possess a very pungent odor which, at the same time, is reminiscent of decaying fungus (53).

### *Patents*

U. S. patent 1,696,539 was issued December 25, 1928 to D. B. Bradner for the purification of diphenylaminechloroarsine. The crude arsine is melted and poured into water and the mass agitated until it solidifies (19).

Bradner (18) received U. S. patent (reissue) 16,841, January 3, 1928, for the means of volatilizing diphenylaminechloroarsine and other irritating substances by passing a stream of hot products of combustion over the surface of the material to volatilize it.

### *Physiological action*

The physiological action of the arsenical compounds consists of irritation of the nose, throat, eyes, and lungs, causing hyperemia and congestion. There is a feeling of suffocation, nausea, and vomiting. Following these initial symptoms, numbness of the limbs may occur, which may terminate in sharp pains of the legs and toes.

Following the acute symptoms there may be slight dizziness, headache, and effects on the nervous system consisting of sensory and motor disturbances. Anesthesia varying from mere numbness of the finger tips to a complete loss of sensation over a considerable part of one or more limbs is occasionally observed. In some instances paralysis may result. It is the opinion of observers that the motor or sensory nerve changes are functional in character, inasmuch as recovery from these conditions is rapid and uniform.

The respiratory tract may also be affected by the arsenical compounds; the mucous membrane of the nose, throat, and bronchi may be involved and there may be edema of the lungs. In this respect the physiological action of the arsenical compounds is similar to that of chlorine and phosgene, with the additional epithelium-destroying properties of "mustard." The edema produced by the arsenicals is not as severe as that resulting from phosgene poisoning. The destruction of the bronchial epithelium does not extend down the respiratory tract to the small divisions of the bronchial tree, as is the case in mustard poisoning. Irritation of the skin is not as severe as that following mustard gas poisoning, but the skin damage is more severe than that due to chlorine or phosgene. The acute inflammatory reaction of the eyes due to arsenical compounds is severe but rarely as permanent as that following gassing with mustard (57).

Winternitz (149) in experimental work with methyl-, ethyl-, and phenyl-dichloroarsines and their effect on animals, found that the principal toxic action was on the respiratory tract. Here these arsenicals caused a severe congestion of the larynx and trachea, with the production of a good deal of exudate. In addition the mucous membrane of the bronchi is congested, with the production of exudate which may occlude their lumen.

In the lungs the arsenical compounds produced congestion as well as edema. There were scattered areas of focal pneumonia which terminated in pus formation. Atelectasis as well as emphysema were found in the lung tissue. Congestion of the liver and spleen, as well as ulceration of the gastrointestinal tract, have been noted following gassing with arsenical compounds. The kidneys and liver show evidence of hemorrhagic changes as well as epithelial degeneration.

In addition, arsenical compounds gave evidence of skin-irritant properties which were not, however, as severe as the destruction of the skin caused by mustard. Animals subjected to the action of arsenical compounds show evidence of congestion of the eyes, which was not as severe as that caused by mustard.

Inhalation of these arsenical compounds was followed by sneezing, nausea, vomiting, pain in the chest and abdomen, and conjunctivitis. The full action of poisoning with arsenical compounds became intense within a short space of time, and disablement resulted even from the inhalation of a weak concentration of the poison. Upon swallowing arsenical compounds evidence of acute gastritis and enteritis was noted.

The pathological lesions resulting from gassing with arsenical compounds consist of the following: There may be intense involvement of the entire respiratory tract, beginning with the larynx and trachea and terminating in the fine bronchioles and air sacs. The inflammatory reaction consists of a more or less yellowish, fibrinopurulent exudate. The bronchioles show the presence of exudate and edema fluid which may occlude the lumen. The lungs are voluminous and heavier and firmer than normal with areas of edema, congestion, atelectasis, and emphysema. Scattered patches of focal pneumonia with or without pus formation may be seen. Scattered hemorrhages, both pulmonary and subpleural, are noted where the edema is considerable and the smaller bronchi are blocked.

In reviewing the post-mortem findings of the men who were gassed with arsenical compounds and who died immediately after gassing, it was found that bronchopneumonia and lobar pneumonia were the two principal causes of death.

Of the men who were gassed with arsenical compounds and who survived the gassing, but who gave evidence of residual disabilities and who died subsequently, the post-mortem findings showed that bronchopneumonia was the direct cause and chronic bronchitis the contributory cause of death.

Microscopically, the important changes following gassing with arsenical compounds are in the respiratory tract. The mucous membrane of the trachea was found to contain a fibrin network with large spaces full of edema fluid. The epithelial lining of the trachea was found to be lifted. In the early stages there was little polymorphonuclear infiltration, but this became more marked in a short time.

In the lungs the microscopic changes showed areas of congestion and edema interspersed with areas showing alveoli overdistended with air. The capillaries of the alveolar walls, particularly in the edematous areas, were tortuous and filled with red blood cells. The alveolar epithelium seemed to suffer very little and in most places was intact. In places much fibrin could be seen in the edematous alveoli. The bronchi showed a continuation of the findings in the tracheal mucous membrane, but the bronchioles usually presented an intact layer of epithelium.

Ulceration of the mucous membrane of the gastrointestinal tract was observed in some instances. Other organs, such as the liver, kidneys, and spleen, showed but little pathological changes. There was slight swelling and granulation of the parenchymal cells.

Animals that survive the acute effects of gassing with the arsenicals may show such complications as suppurative bronchitis, bronchopneumonia, or suppurative pleurisy.

#### REFERENCES

- (1) AESCHLIMANN: J. Chem. Soc. **1927**, 413-7.
- (2) AESCHLIMANN: J. Chem. Soc. **127**, 811-5 (1925).
- (3) ANONYMOUS: Gasschutz u. Luftschutz **2**, 264 (1932).
- (4) AUGER: Compt. rend. **138**, 1705-7 (1904).
- (5) AUGER: Compt. rend. **142**, 1151-3 (1906).
- (6) AUGER AND BILLY: Compt. rend. **139**, 597-9 (1904).
- (7) VON AUWERS: Ber. **53**, 941-4 (1920).
- (8) VON AUWERS: Ber. **58**, 543-4 (1925).
- (9) BAEYER: Ann. **107**, 257-93 (1858).
- (10) BAUD: Compt. rend. **130**, 1319-22 (1900).
- (11) VON BAYER: Chem. Zentr. **86**, I, 72 (1915).
- (12) BAXTER, BEZZENBERGER, AND WILSON: J. Am. Chem. Soc. **42**, 1386-93 (1920).
- (13) Blicke, Patelski, and Powers: J. Am. Chem. Soc. **55**, 1158-61 (1933).
- (14) Blicke and Powers: J. Am. Chem. Soc. **54**, 3353-60 (1932).
- (15) Blicke and Powers: J. Am. Chem. Soc. **55**, 1161-7 (1933).
- (16) Blicke and Smith: J. Am. Chem. Soc. **51**, 1558-65 (1929).
- (17) BORGER AND GROLL: Krankheitsforsch. **2**, 220-62 (1926).
- (18) BRADNER: Chem. Abstracts **22**, 999 (1928).
- (19) BRADNER: Chem. Zentr. **100**, I, 1511 (1929).
- (20) BURROWS AND TURNER: J. Chem. Soc. **117**, 1373-83 (1920).
- (21) BURTON AND GIBSON: J. Chem. Soc. **125**, 2275-8 (1924).
- (22) BURTON AND GIBSON: J. Chem. Soc. **1926**, 450-64.
- (23) BURTON AND GIBSON: J. Chem. Soc. **1926**, 464-70.
- (24) BURTON AND GIBSON: J. Chem. Soc. **1926**, 2241-7.

- (25) BURTON AND GIBSON: *J. Chem. Soc.* **1927**, 247-50.
- (26) CARR: *J. Soc. Chem. Ind.* **38**, 468R (1919).
- (27) CHALLENGER AND PRITCHARD: *J. Chem. Soc.* **125**, 864-75 (1924).
- (28) CHALLENGER AND RIDGWAY: *J. Chem. Soc.* **121**, 104-20 (1922).
- (29) CONTARDI: *Giorn. chim. applicata* **1**, 11-26 (1920).
- (30) CONTARDI: *Giorn. chim. applicata* **2**, 100-11 (1920).
- (31) DAFERT: *Monatsh.* **40**, 313-23 (1919).
- (32) DEHN: *Am. Chem. J.* **33**, 101-53 (1905).
- (33) DEHN: *Am. Chem. J.* **40**, 88-127 (1908).
- (34) DEHN AND McGRATH: *J. Am. Chem. Soc.* **28**, 347-61 (1906).
- (35) DEHN AND WILCOX: *Am. Chem. J.* **35**, 1-54 (1906).
- (36) ELSON AND GIBSON: *J. Chem. Soc.* **1931**, 294-305.
- (37) ELSON, GIBSON, AND JOHNSON: *J. Chem. Soc.* **1929**, 1080-8.
- (38) FISCHER: *Ann.* **403**, 106-17 (1914).
- (39) FISCHER: *Mikrochemie* **12**, 257-60 (1932).
- (40) FLEURY: *Bull. soc. chim.* **27**, 699-704 (1920).
- (41) FLURY: *Z. exptl. Med.* **13**, 523-78 (1921).
- (42) FOULERTON: *J. Path. Bact.* **24**, 257-71 (1921).
- (43) FRAHM AND BOOGAERT: *Rec. trav. chim.* **49**, 623-6 (1930).
- (44) GANGLOFF AND HENDERSON: *J. Am. Chem. Soc.* **39**, 1420-7 (1917).
- (45) GIBSON, HISCOCKS, JOHNSON, AND JONES: *J. Chem. Soc.* **1930**, 1622-32.
- (46) GIBSON AND JOHNSON: *J. Chem. Soc.* **1927**, 2499-516.
- (47) GIBSON AND JOHNSON: *J. Chem. Soc.* **1928**, 92-9.
- (48) GIBSON AND JOHNSON: *J. Chem. Soc.* **1928**, 2204-15.
- (49) GIBSON AND JOHNSON: *J. Chem. Soc.* **1929**, 767-87.
- (50) GIBSON AND JOHNSON: *J. Chem. Soc.* **1929**, 1229-62.
- (51) GIBSON AND JOHNSON: *J. Chem. Soc.* **1929**, 1621-2.
- (52) GIBSON AND JOHNSON: *J. Chem. Soc.* **1931**, 753-6.
- (53) GIBSON AND JOHNSON: *J. Chem. Soc.* **1931**, 2518-23.
- (54) GIBSON AND JOHNSON: *J. Chem. Soc.* **1931**, 3270-3.
- (55) GIBSON, JOHNSON, AND VINING: *Rec. trav. chim.* **49**, 1006-35 (1930).
- (56) GIBSON AND VINING: *J. Chem. Soc.* **125**, 909-11.
- (57) GILCHRIST AND MATZ: *Med. Bull. Veterans' Admin.* **10**, 79-98 (1933).
- (58) GODDARD: *A Textbook of Inorganic Chemistry*. Chas. Griffin and Co., London (1930).
- (59) GODDARD, ASHLEY, AND EVANS: *J. Chem. Soc.* **121**, 978-82 (1922).
- (60) GORSKIĭ, SHPANSKIĭ, AND MULYAR: *Ber.* **67**, 730-5 (1934).
- (61) GREEN AND PRICE: *J. Chem. Soc.* **119**, 448-53 (1921).
- (62) GRYSZKIEWITZ-TROCHIMOWSKI, MATEYAK, AND ZABLOTSKI: *Bull. soc. chim.* [4] **41**, 1323-33 (1927).
- (63) GRYSZKIEWITZ-TROCHIMOWSKI AND SIKORSKI: *Bull. soc. chim.* [4] **41**, 1570-85 (1927).
- (64) HANZLIK AND TARR: *J. Pharmacol.* **14**, 221-8 (1920).
- (65) HENLEY AND SUGDEN: *J. Chem. Soc.* **1929**, 1058-65.
- (66) HERBST: *Kolloidchem. Beihefte* **23**, 313-44 (1926).
- (67) JOB AND GUNOT: *Chem. Zentr.* [4] **92**, 870-1 (1921).
- (68) JOHNSON: *Ber.* **65**, 294-302 (1932).
- (69) JONES, DYKE, DAVIS, GRIFFITHS, AND WEBB: *J. Chem. Soc.* **1932**, 2284-93.
- (70) KAPPELMEIER: *Rec. trav. chim.* **49**, 57-85 (1930).
- (71) KAPPELMEIER: *Rec. trav. chim.* **60**, 44-50 (1931).
- (72) KRETOV AND BERLIN: *J. Gen. Chem. U.S.S.R.* **1**, 411-8 (1931).

- (73) LACOSTE: *Ann.* **208**, 1-36 (1881).
- (74) LACOSTE AND MICHAELIS: *Ber.* **11**, 1883-7 (1878).
- (75) LACOSTE AND MICHAELIS: *Ann.* **201**, 184-261 (1880).
- (76) LANDOLT: *Ann.* **92**, 365-71 (1854).
- (77) LANDOLT: *J. prakt. Chem.* **63**, 283-9 (1854).
- (78) LEWIS AND HAMILTON: *J. Am. Chem. Soc.* **43**, 2218-23 (1921).
- (79) LEWIS, LOWRY, AND BERGEIM: *J. Am. Chem. Soc.* **43**, 891-6 (1921).
- (80) LEWIS AND PERKINS: *J. Ind. Eng. Chem.* **15**, 290-5 (1923).
- (81) LEWIS AND STIEGLER: *J. Am. Chem. Soc.* **47**, 2546-55 (1925).
- (82) LEWIS AND STIEGLER: *J. Am. Chem. Soc.* **52**, 4164 (1930).
- (83) LUSTIG: *Sperimentale* **86**, 155-73 (1932).
- (84) MCKENZIE AND WOOD: *J. Chem. Soc.* **117**, 406-15 (1920).
- (85) MANIER AND MORELLI: *Sperimentale* **83**, 45-62 (1929).
- (86) MANN AND POPE: *J. Chem. Soc.* **121**, 1754-9 (1922).
- (87) MATSUMIYA: *Mem. Coll. Sci. Kyoto Imp. Univ.* **4**, 217-23 (1920).
- (88) MICHAELIS: *Ber.* **8**, 1316-7 (1875).
- (89) MICHAELIS: *Ber.* **9**, 1566-9 (1876).
- (90) MICHAELIS: *Ann.* **321**, 141-248 (1902).
- (91) MICHAELIS: *Ber.* **41**, 1514-6 (1908).
- (92) MICHAELIS AND LINK: *Ann.* **207**, 193-219 (1881).
- (93) MICHAELIS AND REESE: *Ber.* **15**, 2876-7 (1882).
- (94) MICHAELIS AND ROBINSON: *Ann.* **270**, 139 (1892).
- (95) MIELENZ: *Gasschutz u. Luftschutz* **2**, 10-4 (1932).
- (96) MORGAN AND VINING: *J. Chem. Soc.* **117**, 777-83 (1920).
- (97) NAMETKIN AND NEKRASOV: *Z. anal. Chem.* **77**, 285-9 (1929).
- (98) NEKRASOV AND NEKRASOV: *Ber.* **61**, 1816-21 (1928).
- (99) NORRIS: *J. Ind. Eng. Chem.* **11**, 817-29 (1919).
- (100) OECHSLIN: *Chem. Zentr.* **93**, IV, 945 (1922).
- (101) PALMER: *Ber.* **27**, 1378-9 (1894).
- (102) PALMER AND DEHN: *Ber.* **34**, 3594-9 (1901).
- (103) POPE AND TURNER: *J. Chem. Soc.* **117**, 1447-52 (1920).
- (104) QUICK AND ADAMS: *J. Am. Chem. Soc.* **44**, 805-16 (1922).
- (105) RAZUVAEV: *Ber.* **62**, 605-16 (1929).
- (106) RAZUVAEV: *Ber.* **62**, 1208-20 (1929).
- (107) RAZUVAEV: *Ber.* **62**, 2675-7 (1929).
- (108) RAZUVAEV: *Ber.* **63**, 343-6 (1930).
- (109) RAZUVAEV: *Ber.* **64**, 2860-3 (1931).
- (110) RAZUVAEV AND BENEDIKTOV: *J. Russ. Phys. Chem. Soc.* **62**, 549-54 (1930).
- (111) RAZUVAEV, GODINA, AND YEMEL'YANOVA: *Ber.* **65**, 666-72 (1932).
- (112) RAZUVAEV AND KOTON: *J. Gen. Chem. U.S.S.R.* **2**, 529-33 (1932).
- (113) RAZUVAEV AND KOTON: *J. Gen. Chem. U.S.S.R.* **2**, 889-92 (1932).
- (114) RAZUVAEV AND MALINOVSKII: *Ber.* **64**, 120-30 (1931).
- (115) ROEDER AND BLASÉ: *Ber.* **47**, 2748-52 (1914).
- (116) RONA: *Z. exptl. Med.* **13**, 16-30 (1921).
- (117) ROVIDA: *Sperimentale* **80**, 5-24 (1926).
- (118) ROVIDA: *Sperimentale* **83**, 101-13 (1929).
- (119) ROVIDA: *Sperimentale* **83**, 114-20 (1929).
- (120) SCHERLIN AND EPSTEIN: *Ber.* **61**, 1821-5 (1928).
- (121) SCHMIDT: *J. Am. Chem. Soc.* **43**, 2449-54 (1921).
- (122) SCHMIDT, STEINDORFF, FLUSS, AND SCHAFFRATH: *Chem. Zentr.* **97**, I, 2046 (1926).



- (123) SEIDE AND GORSKI: Ber. **62**, 2186-91 (1929).
- (124) SERGEEV AND GORSKIĭ: J. Gen. Chem. U.S.S.R. **1**, 263-71 (1931).
- (125) SHERLIN AND YAKUBOVICH: J. prakt. Chem. **138**, 23-41 (1933).
- (126) SHIVER: J. Chem. Education **7**, 95-108 (1930).
- (127) STEINKOPF, DONAT, AND JAEGER: Ber. **55**, 2597-614 (1922).
- (128) STEINKOPF AND DUDEK: Ber. **62**, 2494-7 (1929).
- (129) STEINKOPF, DUDEK, AND SCHMIDT: Ber. **61**, 1911-8 (1928).
- (130) STEINKOPF AND MIEG: Ber. **53**, 1013-7 (1920).
- (131) STEINKOPF, SCHUBART, AND ROCH: Ber. **65**, 409-12 (1932).
- (132) STEINKOPF, SCHUBART, AND SCHMIDT: Ber. **61**, 678-82 (1928).
- (133) STEINKOPF AND SCHWEN: Ber. **54**, 1437-65 (1921).
- (134) STEINKOPF AND SCHWEN: Ber. **54**, 2791-801 (1921).
- (135) STEINKOPF AND SMIE: Ber. **59**, 1453-63 (1926).
- (136) STOLTZENBERG: Chem. Zentr. **100**, I, 287 (1929).
- (137) STOLTZENBERG: Was jeder vom Gaskampf und den chemischen Kampfstoffen wissen sollte. Hamburg (1930).
- (138) STURNIOLO AND BELLINZONI: Boll. chim. farm. **58**, 409-10 (1919).
- (139) STURNIOLO AND BELLINZONI: Gazz. chim. ital. **49**, ii, 326-7 (1919).
- (140) TANNER: J. Ind. Eng. Chem. **17**, 167 (1925).
- (141) TANNER: Chem. Zentr. **97**, I, 1714 (1926).
- (142) TANNER: Chem. Zentr. **99**, I, 1319-20 (1928).
- (143) UHLING AND COOK: J. Ind. Eng. Chem. **11**, 105-9 (1919).
- (144) VEDDER: The Medical Aspects of Chemical Warfare Williams & Wilkins Co., Baltimore (1925).
- (145) WALKER: J. Chem. Soc. **127**, 1491 (1925).
- (146) WALTON AND ELDRIDGE: J. Pharmacol. **35**, 241-56 (1929).
- (147) WIELAND: Ann. **431**, 30-40 (1923).
- (148) WIELAND AND RHEINHEIMER: Ann. **423**, 1-38 (1921).
- (149) WINTERNITZ: Collected Studies on the Pathology of War Gas Poisoning. Yale University Press, New Haven, Conn. (1920).
- (150) YAKUBOVITSCH: J. prakt. Chem. **138**, 159-66 (1933).
- (151) ZAPPI: Anales asoc. quím. Argentina **3**, 447-50 (1915).
- (152) ZAPPI: Bull. soc. chim. **19**, 151-4 (1916).
- (153) ZAPPI: Bull. soc. chim. **19**, 290-300 (1916).
- (154) ZAPPI: Bull. soc. chim. **23**, 322-4 (1918).
- (155) ZAPPI AND DEULOFEU: Bull. soc. chim. **43**, 1230-2 (1928).
- (156) ZAPPI AND DEULOFEU: Anales asoc. quím. Argentina **17**, 59-62 (1929).
- (157) ZEIDE, SHERLIN, AND BRAS: J. prakt. Chem. **138**, 225-30 (1933).

# INDUCED PRECIPITATIONS AND PROPERTIES OF METAL SULFIDES

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## EXAMPLES OF INDUCED PRECIPITATIONS

It has been frequently observed that in separations of the metals of the second and third groups of the qualitative analysis scheme the metal sulfides of group II may cause the appearance of the sulfides of group III in the precipitate under conditions which would not allow the precipitation of the latter if present alone. Such phenomena have been vaguely referred to as examples of "induced" precipitation, and various cases have been investigated and discussed. Conflicting views as to the nature of the phenomena have resulted and the matter at present is in a state of considerable dispute.

Among the observations reported which are clearly defined examples of the above-mentioned effect, or which seem to have some bearing on the subject, the following may be briefly listed.

The case of the sulfides of copper and zinc has received much attention by workers in the field of analytical chemistry. It has been known for a long time that zinc sulfide is "carried down" by copper sulfide when precipitation by hydrogen sulfide takes place at such an acidity that zinc sulfide would not precipitate from solutions containing only zinc salts. A review of the literature reveals that notice was taken of the difficulty met with in separating zinc and copper by the sulfide method as early as the middle of the nineteenth century by Rivot and Boquet (62), Calvert (15), Spigatus (72), and Grundmann (29). Further investigations regarding this pair have been made by Baubigny (7), Larsen (50), Berglund (8), Glixelli (26), Kolthoff and Van Dijk (45), Böttger and Druschke (11), and Kolthoff and Pearson (46).

Craig (16) found difficulty in recovering small quantities of cadmium in sulfide zinc ores, since in hydrochloric acid medium it was necessary to keep the acidity so high in order to prevent precipitation of the zinc that the cadmium was incompletely precipitated. The limiting acidity at which the separation could be effected was found to be 1.8 *N* in sulfuric acid,—an acidity far greater than that necessary to prevent precipitation

of zinc sulfide from solutions containing salts of that element alone. This behavior is related to the observation made by Treadwell and Guiterman (77) that zinc sulfide is carried down by cadmium sulfide.

Feigl (19) mentions that mercuric sulfide precipitated from an acid solution (acidity not given) in the presence of zinc ions contains about 3 per cent zinc sulfide. Related to the subject is the statement by Hillebrand and Lundell (36) that the separation of mercury from most members of the hydrogen sulfide group, based on the insolubility of mercuric sulfide in boiling dilute nitric acid, fails if the mercuric sulfide is brought down in solutions containing copper, cadmium, or zinc. It was found by the present authors that mercuric sulfide does have a tremendous promoting effect on the precipitation of zinc sulfide, and a detailed investigation of the phenomenon in the case of these two sulfides has been made (59).

The precipitation of zinc sulfide has also been found to be hastened by the sulfides of lead or tin (51) and by arsenic pentasulfide (21). From work being done at present in this laboratory by Mr. Griffith it may be stated that bismuth sulfide has a similar effect.

On the other hand, Funk (24) reports that manganese, cobalt, nickel, and iron are carried out of acetic acid solution with zinc sulfide by precipitation with hydrogen sulfide, even though those ions if present alone in acetic acid medium are not precipitated as sulfides. A similar observation as to the "induced" precipitation of the sulfides of nickel and cobalt with zinc sulfide has been made by Kato (40) and by Kling, Lassieur, and Lassieur (41).

Auger and Odinet (3) found that even at an acidity where stannic tin is incompletely precipitated by hydrogen sulfide, cobalt sulfide is found in the precipitate if precipitation takes place from a solution containing ions of both metallic elements. Divalent tin seemed to have no such effect. It also appears that iron sulfide is carried down from acid solution by stannic sulfide, and that nickel sulfide is brought down by stannous sulfide (21).

Berglund (8) reported that cadmium sulfide is carried down by copper sulfide in strongly acid solution.

Böttger and Druschke (11) found that even in 3 *N* nitric acid solution a precipitate of copper sulfide is contaminated with an appreciable amount of iron sulfide if precipitation takes place from a solution containing salts of both metals.

The above authors, in common with Manchot, Grassl, and Schneeberger (56) and Feigl (19), found that a much greater concentration of hydrochloric acid is required in the separation if mercuric chloride is present than that required to prevent precipitation of cadmium sulfide alone. Rosenblatt (64), too, found difficulty in effecting this separation. A similar phenomenon has been noted in the case of mercury and copper (21).

Thalious sulfide, which is not precipitated from mineral acid solution by the action of hydrogen sulfide, was found to be "carried down" by the sulfides of arsenic, antimony, tin, lead, mercury, and copper (13, 33, 40).

Tungsten sulfide, though easily soluble in alkali sulfides, owing to the formation of thiotungstates, is brought down by the addition of ammonium sulfide to a solution which contains, besides tungsten, other cations, such as manganese, which are precipitated by that reagent (21).

Platinum sulfide, while only incompletely precipitated by hydrogen sulfide from acid solution, nevertheless "induces" sulfide precipitation of metals not usually precipitated if present alone. This effect is especially marked in the case of iron (21).

Working in basic solution Feigl (20) found that the sulfides of cadmium, zinc, and manganese removed appreciable quantities of mercury from solutions of sodium mercuric sulfide ( $\text{Na}_2\text{HgS}_2$ ). If manganous sulfide is precipitated with zinc sulfide or mercuric sulfide, the precipitate cannot be freed of manganese by treatment with acetic acid. Likewise if mercuric sulfide is precipitated on the sulfides of manganese, zinc, or cadmium and extracted with sodium sulfide, some mercury is left in the residue. This observation has been confirmed by the present authors.

#### INTERPRETATION OF THE INDUCED SULFIDE PRECIPITATIONS

The above list of instances where the "carrying down" effect would appear to be indicated serves to illustrate the wide occurrence of the phenomenon. It is not to be assumed, however, that all cases occur according to one general process or mechanism. Even in the case of one particular pair of metal sulfides there may be several effects involved which give rise to the composite effect designated as "induced" precipitation. Various theories have been advanced to explain the phenomenon in certain specific cases.

Bassett (6) proposes that in the precipitation of metallic sulfides from acid solution with hydrogen sulfide, amphoteric neutralization of the primarily formed hydrosulfides occurs, resulting in the formation of the sulfide precipitate from molecular complexes of the hydrosulfides with elimination of hydrogen sulfide. This theory in the case of sulfides is based on analogy with amphoteric neutralization processes proposed in regard to the hydroxides of copper and other metals. Bassett further suggests that such a mechanism is partly responsible for the readiness with which certain sulfides, notably copper, carry down from acid solutions sulfides of the third group such as zinc. There seems to be no definite proof, however, that the formation of sulfide precipitates involves amphoteric neutralization as proposed, or that contamination of a sulfide

precipitate of the second group by sulfides of the third group is even partially a consequence of such a mechanism.

Feigl (19, 20, 21) attempted to clear up the entire problem of induced precipitations among the sulfides by his Coördination Theory. Rejecting the ionic theory and the law of mass action as regards the precipitation of sulfides, he proposes that by virtue of the residual valences on the sulfur atoms the following types of coördination compounds may be obtained: (1)  $MS-SH_2$ , hydrosulfide; (2)  $MS-S$ , polysulfide; (3)  $M_1S-SM_1$ , isopolymer; (4)  $M_1S-SM_2$ , heteropolymer or mixed sulfide. Cases such as we are considering are then represented according to Feigl by type 4.

It is evident from consideration of this theory that Feigl assumes a condition of coprecipitation in all cases. Undoubtedly Feigl is wrong in his generalization, although the existence of compound formation among the sulfides cannot be successfully disputed. Examples in the case of copper and thallium, mercury and manganese, possibly in the case of copper and iron and others have been reported by various investigators (13, 81, 33, 35, 69). In general, however, Feigl's views have not been favorably received by other workers in the field.

By the powder method of x-ray analysis Böttger and Druschke (11) were unable to detect any evidence of compound formation in the sense of Feigl in the case of the sulfides of mercury and cadmium. In the later work of Böttger and Ahrens (1) the belief was again expressed that Feigl's theory could not explain the "carrying down" effect exhibited by these two sulfides.

Weiser (81) expresses the opinion that while the existence of mixed salts such as  $2HgS \cdot MnS$  cannot be denied, it is probable that most instances of contamination such as are here considered are due to adsorption phenomena.

Kolthoff and Pearson (46) concluded Feigl's theory to be untenable in the case of copper and zinc sulfides, and the same conclusion is just as strongly supported in the case of mercury and zinc (59).

Ruff and Hirsch (66) have vigorously attacked both the theory and experimental evidence cited by Feigl. They contend that the mass action law and solubility product principles are the decisive factors in separations of the sulfides, and that occlusion, adsorption, and mixed crystal formation are of only minor importance. In polemical papers Feigl (20) as well as Ruff (65, 66) defended their antagonistic viewpoints without changing any of their former statements. The contentions of Ruff and Hirsch are somewhat weakened, however, by lack of consistency and clarity in some of the explanations advanced by them to interpret Feigl's results and also by lack of experimental evidence in support of their own theories. These investigators have advanced the hypothesis that a protective coating of

the sulfide with the smaller solubility product may be formed about the sulfide with the larger solubility product. In order to explain the promoting effect of such substances as copper sulfide or mercuric sulfide on the precipitation of zinc sulfide, this theory necessitates the condition that the less soluble sulfide be deposited on the more soluble one. This condition is not realized in the instances mentioned, since it has been shown that the more insoluble sulfide is quantitatively precipitated in a pure form before any zinc sulfide enters the precipitate (46, 59). Böttger and Ahrens (1) concluded that the theory of Ruff and Hirsch was not acceptable as an explanation of the induced precipitation effect in the case of the sulfides of mercury and cadmium.

Balarew (4) indicates that the "carrying down" of zinc sulfide by other sulfides may be explained by his theory of "inner adsorption." According to his view macro crystals having a mosaic structure are formed by the building on of primary building blocks or submicroscopic crystals to other such crystal entities to give rise to a network of capillaries within the crystal aggregate. It is in these capillaries that adsorbed material may then be held. It follows that, according to Balarew, the "carrying down" of zinc sulfide would then be a wholly capillary phenomenon, similar to the coprecipitation of potassium permanganate with barium sulfate. Balarew reports that he was unable to extract completely the zinc from a copper sulfide-zinc sulfide "mixed" precipitate even with strong hydrochloric acid. This result is contradictory to the results of Kolthoff and Pearson, as well as to those of Böttger and Druschke, and on the whole Balarew's experimental work in regard to the sulfides of copper and zinc seems to be somewhat questionable.

Böttger and Druschke (11) and also Ahrens (1), working with the pairs Cu-Fe, Cu-Zn, and Hg-Cd, seem to have regarded the phenomenon in all these cases as one of coprecipitation. They found surprising difficulty in extracting iron from the Cu-Fe "mixed" sulfide. Likewise cadmium could not be completely removed except by drastic treatment from a precipitate obtained by precipitating mercuric and cadmium sulfides together. A similar behavior has been noted by the present authors in the case of the sulfides of mercury and zinc. However, in harmony with the work of Kolthoff and Pearson, Böttger and Druschke were able to extract completely the zinc from corresponding Cu-Zn precipitates by treatment with 1 *N* hydrochloric acid solution, and they assumed the viewpoint that in the cases of Cu-Zn and Hg-Cd, at least, a kind of isomorphous replacement or mixed crystal formation had taken place. From the work of Ahrens on the Hg-Cd couple it was concluded that the coprecipitation effect was to be attributed to a mixed crystal formation. Böttger and Druschke explained the difference in ease of extraction of the more soluble

sulfides in the two respective cases as being a consequence of the extent to which the more insoluble sulfide was attacked by the acid. However, the behavior of the mixed precipitate of copper and iron sulfides as regards extraction is not consistent with this explanation.

The view is quite generally taken, though in many cases not definitely proven, that mixed crystal formation exists as a partial explanation of the phenomenon in many cases. Undoubtedly mixed crystal formation among the sulfides is of frequent occurrence, since the similarity in structure and ionic domains (both as to size and shape) exhibited by different sulfides makes this event seem highly probable. Mention of this effect in the instance of the sulfides of mercury and cadmium as reported by Böttger and Ahrens has already been made. X-ray evidence of mixed crystal formation in the cases of the sulfides of manganese and cadmium and of manganese and zinc has recently been offered by Schnaase (68). It was found that the former pair formed a continuous series of mixed crystals of the zinc blende type, and that a like series having the wurtzite structure was indicated. Under the conditions of precipitation employed in the case of the sulfides of manganese and zinc, a miscibility gap extending from about 20 to 84 atomic per cent manganese was indicated. Precipitates having compositions corresponding to this gap were found to consist of two separate phases having compositions corresponding to the above limits. Such mixed crystals were predominantly of the zinc blende type, although some having a wurtzite structure were also present. No indication of mixed crystal formation was found by Kolthoff and Pearson (46) in their work on the sulfides of copper and zinc. In the case of mercury and zinc sulfides again, evidence of a limited mixed crystal formation was obtained (59).

The above serves to illustrate the frequency with which the effect is encountered. However, it is believed that even in cases where mixed crystal formation does occur, this phenomenon may be a secondary effect and not of primary importance in the depiction of the mechanism by which "induced precipitation" takes place.

It is to be emphasized that in all the papers discussed the viewpoint was held that "induced precipitation" is a matter of coprecipitation. However this condition is not generally realized, since it has been definitely shown in the case of copper and zinc by Kolthoff and Pearson (46) and in the case of mercury and zinc by the present authors (59), that we are not dealing with a coprecipitation but with a postprecipitation. The sulfide with the smaller solubility product (copper sulfide or mercuric sulfide, respectively) primarily precipitates free from zinc, but on standing in the presence of a solution of a zinc salt containing an excess of hydrogen sulfide, more and more zinc sulfide enters the precipitate. From work now being

done in this laboratory by Mr. Griffith, it may be said that a similar statement can be made in the case of bismuth and zinc. The fact that the process involves postprecipitation is made evident by the following experimental data obtained in the investigation of the sulfides of mercury and zinc.

Mixtures of mercuric chloride and zinc sulfate in varying concentrations of hydrochloric acid and mixtures of mercuric perchlorate and zinc sul-

TABLE 1

*Postprecipitation of zinc sulfide*

25 ml. of 0.05 *M* HgCl<sub>2</sub>; 25 ml. of 0.05 *M* ZnSO<sub>4</sub>; acid as indicated

	TIME SHAKEN	KIND OF ACID	ACIDITY BEFORE PRECIPITATION	ZINC PRECIPITATED
	<i>minutes</i>		<i>N</i>	<i>per cent</i>
Blank* . . . . .	0	H <sub>2</sub> SO <sub>4</sub>	0.30	0
	0	H <sub>2</sub> SO <sub>4</sub>	0.30	65
	30	H <sub>2</sub> SO <sub>4</sub>	0.30	95
Blank* . . . . .	30	H <sub>2</sub> SO <sub>4</sub>	0.30	0
	0	H <sub>2</sub> SO <sub>4</sub>	1.05	15
	30	H <sub>2</sub> SO <sub>4</sub>	1.0	47
	30	H <sub>2</sub> SO <sub>4</sub>	2.0	8.0
	60	H <sub>2</sub> SO <sub>4</sub>	2.0	8.6
	60	H <sub>2</sub> SO <sub>4</sub>	4.0	0
	30	HCl	0.30	0
Blank* . . . . .	0	HCl	0.30	60
	30	HCl	0.30	85
	0	HCl	0.80	10.5
	30	HCl	0.80	22
	120	HCl	0.80	28
	0	HCl	1.0	6.8
	30	HCl	1.0	13
	0	HCl	1.5	1.6
	30	HCl	1.5	2.8
	0	HCl	1.75	0.5
	60	HCl	2.0	0

\* The blanks contained 25 ml. of water in place of 25 ml. of 0.05 *M* mercuric chloride.

fate in dilute sulfuric acid were treated with hydrogen sulfide in such a way that a small part of the mercury remained in the solution. Upon analysis of the filtrate all of the zinc originally present was recovered, thus showing that zinc is not coprecipitated with mercuric sulfide.

The results in table 1, which are substantiated by a great number of experiments at other acidities and times of shaking, show conclusively that we are dealing with a postprecipitation of zinc sulfide on the surface of mercuric sulfide.



Precipitation was effected by a three-minute passage of the gas through the solution, and thereafter the contents of the flask were mechanically shaken under continuous passage of hydrogen sulfide over the solution for the time noted under "time shaken." After this period of shaking the mixtures were filtered, the precipitates washed four times with cold water, and the filtrates analyzed for zinc by the ferrocyanide method (46). The temperature was 25°C.

In showing the presence of a postprecipitation phenomenon, the above results are substantiated by the fact that the effect is qualitatively the same whether the zinc solution is added before or after precipitation of the mercuric sulfide.

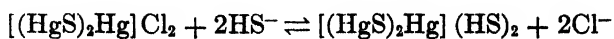
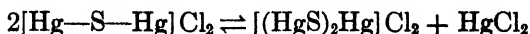
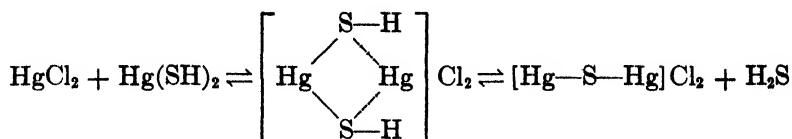
Thus it is shown that freshly precipitated copper sulfide or mercuric sulfide promotes the precipitation of zinc sulfide. This postprecipitation was attributed to the presence of an adsorbed layer of hydrogen sulfide on the copper sulfide and mercuric sulfide, respectively. From colloid chemical studies we know that the metal sulfides exert strongly adsorbent properties towards hydrogen sulfide, hydrosulfide ions, and sulfide ions. Hydrogen sulfide adsorbed on the surface of the metal sulfide has a much stronger tendency to ionize than has that which is present in the bulk of the solution. Thus the concentration of hydrosulfide or sulfide ions in the surface is much greater than in the bulk of the solution, and therefore the speed of precipitation of the more soluble sulfide is much greater at the interface than in the bulk of the solution. The confusing statements found in the literature are mainly to be attributed to the fact that it is generally assumed that the sulfides of the third group are not, or are incompletely, precipitated from weakly acid medium. The fact is overlooked that precipitation equilibrium is sometimes reached only after extremely long periods of standing. Thus, when a solution which is 0.05 *M* with respect to zinc sulfate and 0.5 *N* in sulfuric acid is saturated with hydrogen sulfide, no precipitation occurs for at least forty-five minutes or an hour. With increasing acidity the length of this so-called "induction" period rapidly becomes greater. Employing a solution which was 2 *N* in sulfuric acid and 1/16 *M* with respect to zinc sulfate, Glixelli (26) found that a precipitate was exceedingly slow to appear, but that after a period of two and one-half months precipitation had taken place to the extent of 25 per cent of the original zinc content and that after five months only about 50 per cent remained in solution. It is apparent that the solution tends to remain supersaturated with regard to zinc sulfide. In the presence of mercuric sulfide or copper sulfide, a promoted precipitation takes place by virtue of the presence of the adsorbed hydrogen sulfide.

Before elaborating on some of the interesting phenomena observed in studies of the postprecipitation effect, the mechanism of the precipitation of sulfides and the aging of metal sulfides will first be considered.

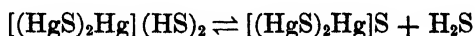
## THE MECHANISM OF THE PRECIPITATION OF SULFIDES

The subject of sulfide precipitation in general presents difficulties in interpretation. Smith (70) calculated that 5 ml. of a 0.2 *N* hydrochloric acid solution which is 0.1 *M* with respect to hydrogen sulfide contains  $3 \times 10^{20}$  non-ionized molecules of hydrogen sulfide,  $15 \times 10^{13}$  hydrosulfide ions ( $\text{SH}^-$ ), and only one sulfide ion ( $\text{S}^{--}$ ). In the precipitation of a very insoluble sulfide such as mercuric sulfide from acid solution by hydrogen sulfide, it would seem impossible for equilibrium to be established in the time in which it is if sulfide ions were directly involved in the reaction. From the considerations mentioned it would seem probable that sulfide precipitation involves the reaction of hydrosulfide ions to give first the hydrosulfide of the metal which, by secondary loss of hydrogen sulfide, results in the formation of the sulfide itself. This view is in harmony with the belief that peptized sulfides are hydrosulfides. While Smith believes that if sulfide formation is to be viewed from an ionic standpoint the hydrosulfide ion rather than the sulfide ion should be regarded as the active precipitating agent, he, like Feigl, tends to favor a non-ionic theory for the process. In a paper by Smith and Semon (71) the opinion is advanced that the precipitation of heavy metals as sulfides will eventually be regarded in the light of the coordination theory of Werner. From their work with mercury salts these authors are led to favor a theory embracing the formation of intermediary hydrosulfide compounds. The presence of excess hydrogen sulfide in freshly precipitated material is explained as its being present partially in the hydrosulfide form, probably as decomposition product of hypothetical, unstable, intermediate hydrosulfide compounds. In the light of the existence of known addition products of salts with sulfides, both organic and inorganic, and in view of the fact that compounds are often present in solution too unstable or relatively too soluble for isolation, Smith and Semon deduce the occurrence of addition reactions analogous to the combination of salts with alkyl sulfides, in which the hydrogen sulfide itself assumes the rôle of the organic sulfide (or mobile hydrogen in place of the alkyl radical). Their observations regarding intermediary compounds in the case of mercury is thought to bear out this contention. It is pointed out that the assumption of hydrosulfide compounds is supported by the existence of analogous hydroxide compounds, the hydrogen being more mobile in the case of the hydrosulfides. To illustrate the formulation of sulfide precipitation under such a theory, we may cite the case of the reaction taking place when hydrogen sulfide is passed into a solution of mercuric chloride. Smith describes the mechanism of the reaction by first assuming the formation of an addition product such as  $[(\text{H}_2\text{S})_n\text{Hg}] \text{HgCl}_4$  which, after conversion into the hydrosulfide,  $\text{Hg}(\text{SH})_2$ , may again react with a molecule of mercuric chloride and subse-

quently result in the precipitation of mercuric sulfide as indicated by the following series of equilibria.

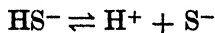


and more slowly



Rather than attributing to a simple adsorption mechanism the inaccuracies found to be due to the coprecipitation of other substances such as chlorides in the determination of mercury by direct precipitation of the sulfide, Fenimore and Wagner (22) suggest that such a theory of intermediate compound formation as outlined above is a more likely interpretation. Weiser and Durham (82), on the other hand, concluded that a like contamination of cadmium sulfide by chloride was due to an adsorption phenomenon.

It should be realized that the assumption of the intermediate formation of coördination compounds is not strictly necessary to explain the rapid precipitation of various metal sulfides. It is true that in the case mentioned by Smith only one sulfide ion was present in 5 ml. of solution, according to the calculation. However, one should not attribute an *absolute* significance to such an "absurdly small concentration." In doing so one would infer that on dividing the 5-ml. portion into two parts, one part would contain one sulfide ion and the other would be free of sulfide ions. This conclusion would, of course, be absurd. In dealing with a reversible reaction such as the dissociation of hydrosulfide ions into sulfide and hydrogen ions,

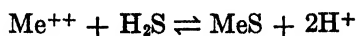


it must be realized that in a given time a certain fraction of the hydrosulfide ions dissociate and that under equilibrium conditions the hydrogen and sulfide ions combine with the same speed to form hydrosulfide ions. We may say that a concentration of one sulfide ion per 5 ml. of solution means that practically all the sulfide ions are present in the associated state and that, averaged over a given time interval, only a very few are present as free ions. In other words, the concentration term in equilib-

rium reactions is a statistical expression which denotes the *probability* that the dissociation and association products are present at a certain concentration at a given instant. If, in a dissociation process, the concentrations of the reaction products are such that they seem realizable according to our general conceptions (e.g., in the dissociation of 0.1 *N* acetic acid) we attribute to the concentrations an *absolute* significance. However, with regard to a system in kinetic equilibrium the concentration is a *relative* concept or, in other words, the concentration is an *abstract* mathematical expression.

According to the above one cannot definitely conclude that the rapid precipitation of metal sulfides in acid medium cannot occur by direct combination of metal and sulfide ions. Many sulfide ions may be formed per second by dissociation of hydrogen sulfide or hydrosulfide ions, most of which, however, disappear with the same speed by recombination with hydrogen ions. In the presence of metal ions which give rise to the formation of slightly soluble sulfides there is a possibility that the sulfide ions formed by dissociation react with the metal ions before they have a chance to associate again with hydrogen ions. Whether such a description of the mechanism is correct is impossible to say, since the individual speeds of reaction are unknown. It also seems possible that the metal sulfide might be formed directly by effective collisions of metal ions with hydrogen sulfide molecules or hydrosulfide ions without assuming the formation of intermediate compounds. Since the speed of formation of metal sulfides in acid medium is inversely proportional to the *square* of the hydrogen-ion concentration, a direct reaction between metal ions and hydrogen sulfide molecules may be excluded from consideration. On the basis of this fact a direct reaction between metal ions and hydrosulfide ions or sulfide ions is possible.

The exact mechanism of the precipitation of metal sulfides in acid medium is immaterial from the viewpoint of the mass action law. This law can be applied to all cases as long as the system is in a state of reversible equilibrium. Various authors (14, 19, 26) have overlooked this simple fact and have been led to express doubt as to the reversibility of the reaction



and to point out apparent contradictions to the mass action law in the case of sulfide precipitations. However, explanations based upon assumptions which are contrary to the law of mass action must result in failure to fulfill their purpose.

Many metal sulfides tend to form supersaturated solutions. This may be explained partly by the relatively large difference in solubility of ex-

tremely small nuclei and crystals of larger size, but mainly by the slow formation of nuclei and the small speed of crystallization. It is well known that relatively weakly acid solutions of zinc, cobalt, and nickel do not precipitate by treatment with hydrogen sulfide in a reasonable length of time, even though the solubility product has been exceeded to a rather large extent. Recognition of the fact that during such a period the system is in a state of supersaturation is of the utmost importance in a study of the promoting effect of certain sulfides on the precipitation of more soluble sulfides. The fact that zinc sulfide, for example, is not quickly and completely precipitated unless the hydrogen-ion concentration is quite low, but that precipitation takes place on long standing from solutions that are quite strongly acid has been shown by various workers (2a, 12, 45) besides Glixelli, to whose experiments reference has been made in a previous paragraph. The phenomenon, often referred to as involving an "induction period," seems not to have been considered from the standpoint of supersaturation by Glixelli.

Analogous behavior as regards such an "induction" period has been pointed out by Baubigny (7), Glixelli (26), Thiel and Ohl (76), and others in the cases of cobalt and nickel sulfides and in the precipitation of cadmium sulfide by Krishnamurti (48). Apparently the induction period in the case of cobalt and nickel may be very long, since under certain conditions of acidity Baubigny found that precipitation was still taking place after a couple of months. Likewise in the case of zinc sulfide a very prolonged induction period may be experienced, while in the case of cadmium sulfide Krishnamurti found that equilibrium was attained within six hours.

Besides demonstrating the increase in the length of the induction period with increasing acidity, Glixelli, whose work provides an admirable statement of the facts to be considered in studies involving promoting effects on the precipitation of zinc sulfide, showed that it was decreased (speed of precipitation of zinc sulfide increased) by the presence of copper sulfide, zinc sulfide, and silica gel. It may be considered as a substantiation of a theory involving surface phenomena, that the effect which zinc sulfide had on the promotion of its further precipitation depended on the nature of the product used, increasing in the order indicated: ignited < aged < fresh. The adsorption of hydrogen sulfide on the given products would increase in like order. In the same work the self-promotive nature of the process (precipitation of zinc sulfide) was clearly shown. Other conditions being equal, precipitation proceeded to a much greater extent in an experiment in which the precipitated zinc sulfide was allowed to accumulate than in one in which the precipitate was successively removed. Koltzoff and Pearson (46) further found that a number of finely divided substances (powdered glass, barium sulfate, sulfur, charcoal, talc, etc.) seemed

to have a definite, though slight, promoting effect on the precipitation of zinc sulfide.

#### THE SOLUBILITY OF METAL SULFIDES

Kolthoff (44) pointed out that there is tremendous confusion in the literature with regard to the solubilities and solubility products of metal sulfides. Their solubilities in pure water are so small that they cannot be determined by direct measurements. It is difficult, if not impossible, to obtain precipitated sulfides in a pure form and to prevent air oxidation when shaken with water. Moreover, the carbon dioxide content of the water has a large effect on the solubility. The values determined by Weigel (80) and cited in most texts should therefore be rejected. Mainly on the basis of the experimental work of Bruner and Zawadsky (13), Moser and Behr (60), and others, Kolthoff (44) has calculated the solubility products of precipitated metal sulfides. A summary is given in table 2 in which  $pL$  is the negative logarithm of the solubility product  $L$ , and  $K$  is the reaction constant as given in the following equations:

$$[Me^{++}] = K \frac{(H^+)^2}{(H_2S)}$$

or (for  $Ag_2S$ ,  $Tl_2S$ , and  $Hg_2S$ )

$$[Me^+] = \sqrt{K \frac{(H^+)^2}{(H_2S)}}$$

$[Me]$  represents the metal-ion concentration in a solution saturated with hydrogen sulfide and the metal sulfide at a hydrogen-ion concentration of 1.

It must be realized that quite generally the solubility of a metal sulfide depends upon its age and the manner of preparation. After the particles have grown to a certain size and are present in the stable modification, the solubility represents a constant and the solubility product principle can be applied to the calculation of the solubility under various conditions. Freshly precipitated sulfides as a rule are not present in the stable form, and therefore exhibit a higher solubility than aged products. These statements will be further enlarged upon in the next chapter. For the above reasons the data given in table 2 cannot be considered entirely conclusive.

#### THE AGING OF METAL SULFIDES

Upon aging of precipitated metal sulfides in the supernatant liquid agglomeration of the particles occurs, resulting in a decrease of the total surface of the precipitate. This, for example, is demonstrated by the experiments of Freundlich and Schucht (23) with mercuric sulfide obtained

by flocculation of a sol. A large amount of mercuric sulfide sol was mixed with an appropriate amount of neufuchsin (or auramine) solution so that coagulation was complete. The mixture was then stirred in such a way

TABLE 2  
*Solubilities and solubility products of metal sulfides*

METAL SULFIDE	<i>L</i>	p <i>L</i>	<i>K</i>	[Me]	OBSERVER
MnS (flesh colored?) ....	$7.0 \times 10^{-16}$	15.16	$6.3 \times 10^6$	$6.3 \times 10^7$	Bruner and Zawadsky (13)
MnS (green)...	$6.2 \times 10^{-22}$	21.21	5.6	$5.6 \times 10^1$	Moser and Behr (60)
FeS	$3.7 \times 10^{-19}$	18.43	$3.4 \times 10^3$	$3.4 \times 10^4$	Bruner and Zawadsky
FeS	$2.6 \times 10^{-22}$	21.58	2.4	$2.4 \times 10^1$	Moser and Behr
Tl <sub>2</sub> S . . . . .	$7.0 \times 10^{-23}$	22.16	$6.4 \times 10^{-1} (?)$	2.5	Bruner and Zawadsky
Tl <sub>2</sub> S . . . . .	$1.2 \times 10^{-24}$	23.92	$1.1 \times 10^{-2}$	$3.3 \times 10^{-1}$	Moser and Behr
$\alpha$ -ZnS	$8.0 \times 10^{-26}$	25.10	$7.3 \times 10^{-4}$	$7.3 \times 10^{-3}$	Schaefer (67)
$\alpha$ -ZnS	$5 \times 10^{-26}$	25.3	$4.5 \times 10^{-4}$	$4.5 \times 10^{-3}$	Glixelli (26)
$\alpha$ -ZnS	$6.9 \times 10^{-26}$	25.16	$6.3 \times 10^{-4}$	$6.3 \times 10^{-3}$	Moser and Behr
$\beta$ -ZnS . . . . .	$1.1 \times 10^{-24}$	23.96	About $10^{-2}$	$10^{-1}$	Glixelli
CoS . . . . .	$1.9 \times 10^{-27}$	26.72	$1.7 \times 10^{-5}$	$1.7 \times 10^{-4}$	Moser and Behr
NiS . . . . .	$1.1 \times 10^{-27}$	26.96	$1.0 \times 10^{-5}$	$1.0 \times 10^{-4}$	Moser and Behr
CdS (from CdCl <sub>2</sub> ) . . .	$7.1 \times 10^{-28}$	27.15	$6.5 \times 10^{-6}$	$6.5 \times 10^{-5}$	Bruner and Zawadsky
CdS (from CdSO <sub>4</sub> ) . .	$5.1 \times 10^{-29}$	28.29	$4.6 \times 10^{-7}$	$4.6 \times 10^{-6}$	Bruner and Zawadsky
PbS . . . . .	$3.4 \times 10^{-28}$	27.47	$3.1 \times 10^{-6}$	$3.1 \times 10^{-5}$	Bruner and Zawadsky
Bi <sub>2</sub> S <sub>3</sub> . . . . .	$1.6 \times 10^{-72} ?$	71.87	$3.5 \times 10^{-32} ?$	$3.5 \times 10^{-22} ?$	Bernfeld (9)
CuS . . . . .	$6.9 \times 10^{-41}$	40.16	$6.3 \times 10^{-19}$	$6.3 \times 10^{-18}$	Immerwahr (37)
CuS . . . . .	$1.2 \times 10^{-42}$	41.92	$1.1 \times 10^{-20}$	$1.1 \times 10^{-19}$	Knox (42)
CuS . . . . .	$3.5 \times 10^{-42}$	41.46	$3 \times 10^{-20}$	$3 \times 10^{-19}$	Jellinek and Czerwinski (39)
Ag <sub>2</sub> S . . . . .	$1.8 \times 10^{-50}$	49.74	$1.6 \times 10^{-29}$	$4 \times 10^{-14}$	Bernfeld
Ag <sub>2</sub> S . . . . .	$2.3 \times 10^{-51}$	50.64	$2.1 \times 10^{-29}$	$1.45 \times 10^{-14}$	Lucas (55)
Ag <sub>2</sub> S . . . . .	$3.9 \times 10^{-50}$	49.41	$3.6 \times 10^{-28}$	$6 \times 10^{-14}$	Knox
Ag <sub>2</sub> S . . . . .	$1.2 \times 10^{-50}$	49.92	$1.1 \times 10^{-28}$	$3.3 \times 10^{-14}$	Jellinek and Czerwinski
Ag <sub>2</sub> S . . . . .	$5.7 \times 10^{-51}$	50.24	$5.1 \times 10^{-29}$	$2.2 \times 10^{-14}$	Jellinek and Czerwinski
Average Ag <sub>2</sub> S .	$1 \times 10^{-50}$	50.00	$9 \times 10^{-29}$	$3 \times 10^{-14}$	Average
Hg <sub>2</sub> S . . . . .	$1 \times 10^{-47}$	47.0	$0.9 \times 10^{-25}$	$0.95 \times 10^{-12}$	Immerwahr (average)
HgS . . . . .	$3 \times 10^{-54}$	53.5	$2.7 \times 10^{-32}$	$2.7 \times 10^{-31}$	Knox

that the precipitate was kept suspended in the liquid. From time to time a portion was taken out, the mercuric sulfide removed by centrifuging, and the concentration of the dyestuff determined colorimetrically. Employing this procedure they found that the concentration of the dyestuff in

the solution increased with the time; they concluded therefrom that the phenomenon was one of reverse adsorption accompanying the change of mercuric sulfide from an amorphous to a more crystalline form, exhibiting an instance in which a substance has a greater adsorption capacity in the former than in the latter condition. They further found indication that the process was self-promoting and that the addition of crystalline particles of mercuric sulfide to the mixture described above accelerated the reverse adsorption. The effect of temperature on the process was found to be very great. The results of Freundlich and Schucht are not entirely convincing. The rather general observation has been made in this laboratory that the presence of such adsorbed dyestuffs prevents further "aging" of precipitates (47).

In addition to agglomeration a perfection and growth of the crystals of the metal sulfides occur, as is evidenced by a sharpening of the interference lines in x-ray diffraction patterns. Various metal sulfides may be obtained in a state usually designated by the term "amorphous," but may become definitely crystalline on aging in the supernatant liquid. The tendency for the sulfides of the Zn-Cd-Hg family to come down in microcrystalline form increases with increasing atomic number. Böhm and Niclassen (10) report that zinc sulfide precipitated at 0°C. from solutions of zinc sulfate was amorphous, but that after being digested on a water bath for several days an x-radiogram of the product showed sharp interference maxima, indicating that crystallization had taken place. These crystals are submicroscopic since Allen, Crenshaw, and Merwin (2a) found no microscopic evidence of crystal structure of zinc sulfide precipitated and digested under ordinary laboratory conditions. The precipitation of zinc sulfide takes place on long standing from solutions quite strongly acid. Even under such conditions (very slow precipitation at higher acidities), the product contains no crystals of such a size as to be easily visible with a microscope, although such a product, or one obtained by aging, contains larger particles and is much less soluble than zinc sulfide precipitated rapidly at low acidities. In agreement with the observations of Böhm and Niclassen, the present authors found that under the conditions of radiography employed a precipitate of zinc sulfide (from slightly acid solution which had been filtered off and dried immediately after a short precipitation period) gave only a few very faint and diffuse interference maxima, whereas a precipitate which had been aged at room temperature in the supernatant liquid for a period of a month gave a clear and distinct diffraction pattern. A similar contrast in the patterns obtained using fresh and aged mercuric sulfide was noted, though it was indicated that the period of aging necessary before a distinct diffraction diagram could be obtained was shorter in the case of mercuric sulfide than in the case of zinc



sulfide. Apparently aging, in the sense of increased perfection of the agglomerates, does not take place in the dry condition at room temperatures, since the "fresh" precipitates after being kept in the dry condition for two years still gave diffraction patterns consisting of only faint, broad bands with no sharply defined lines in evidence. Under the microscope at a magnification of 440 diameters the aged zinc sulfide appeared to consist mainly of compactly cemented clusters of very small crystals. The clusters were not easily broken up and their appearance and behavior suggested that recrystallization and cementing together had taken place, with the result that the clusters themselves behaved as crystalline entities. The crystals of which these clusters were made up were so small that it was barely possible to distinguish individuals and no crystal faces were apparent. Qualitatively much the same may be said concerning the appearance of the aged mercuric sulfide, though in the precipitates investigated, which were aged for such periods of time and under such conditions as to exclude any appreciable transformation to the trigonal form, the clusters did not seem to be cemented together as firmly nor to as great an extent as in the case of the aged zinc sulfide. The characteristics of the fresh precipitates were rather indefinite, and nothing much can be said about such precipitates, except that the result of clumping together was not as apparent and no indication of the presence of individual crystals could be derived. Such agglomerates as were present were easily broken up,—more so than in the case of the aged products.

Quite generally the growth and perfection of the particles on aging is accompanied by a decrease of the solubility. This observation has been made in the case of zinc sulfide by a number of investigators, including Glixelli (26), Bruner (12), Bruni and Padoa (14), and the present authors. It was found (59) that of two zinc sulfide precipitates from slightly acid solution, one of which was freshly prepared and the other a well-aged product, the respective solubilities in 2 *N* sulfuric acid saturated with hydrogen sulfide were approximately 0.035 *M* and 0.005 *M* with respect to zinc. Moreover, the dependence of the solubility of individual sulfide precipitates upon the conditions under which they are formed has been remarked upon by various investigators. Jeffreys and Swift (38), in investigating the precipitation of zinc sulfide and its separation from other elements, concluded that the hydrogen-ion concentration was the dominant factor governing the form and solubility of the product. Glixelli (26) prepared two zinc sulfide precipitates, one which he designated as  $\alpha$ -ZnS, from acid medium, and the other ( $\beta$ -ZnS) by precipitation with a slight excess of sodium sulfide from a solution of zinc sulfate. The precipitates designated in this way are not to be confused with the wurtzite and zinc blende forms of zinc sulfide which are also designated as  $\alpha$ - and

$\beta$ -ZnS, respectively. It was found that of the two precipitates the one prepared from basic solution was about 4.6 times more soluble than the one obtained from acid medium by precipitation with hydrogen sulfide. However, on continued contact with acid solution retaining the evolved hydrogen sulfide the solubility of the  $\beta$ -ZnS precipitate gradually decreased and approached that of the  $\alpha$ -ZnS precipitate (Glixelli's notation). It follows that precipitates of zinc sulfide formed under varying conditions are not sharply definable from one another, as would be the case of polymorphic substances, and it is apparent that the "solubility" of such products as Glixelli's  $\beta$ -ZnS and the fresh precipitate described in regard to the work of the present authors has little significance, since the precipitate is not present in the stable solid state. Glixelli also reports that zinc sulfide prepared at low temperatures (0°C.) is more soluble than that obtained at higher temperatures. In connection with these studies regarding the dependence of solubility upon the method of preparation, it was also found that the  $\beta$ -ZnS precipitate held water (concluded to be held in an adsorbed state) more tenaciously than the product formed from acid solution. In the interpretation of these results Glixelli favors an explanation which construes the difference in behavior of the two preparations as due to differences in particle size. The above results reported by Glixelli have been confirmed in general by Krokowski (49). Some question arises, however, as to the extent which adsorption of zinc sulfate on the precipitated zinc sulfide might explain the effects observed, since both investigators prepared zinc sulfide from solutions of the sulfate. Work and Odell (83) found that such adsorption was very appreciable in the case of zinc sulfide prepared by the addition of sodium sulfide to zinc sulfate solutions. The conditions under which the latter investigators worked were, however, particularly favorable for the occurrence of such an effect.

In accordance with the observation that the solubility of zinc sulfide preparations depends upon the hydrogen-ion concentration of the solution from which precipitation takes place, Krokowski found that the solubility of the product increased according to the following series. (1) ZnS precipitated with hydrogen sulfide from zinc sulfate solution; (2) ZnS precipitated with hydrogen sulfide from zinc acetate solution; (3) ZnS precipitated with ammonium sulfide from zinc sulfate solution; and (4) ZnS precipitated with hydrogen sulfide from ammoniacal zinc sulfate solution.

That the sulfides of cobalt and nickel after being precipitated and allowed to stand for some time are relatively insoluble in dilute mineral acids, even though these sulfides will not readily precipitate from even very dilute acid solution, is a generally recognized fact. This case has been investigated in some detail by Hertz (34), Thiel and Ohl (76), and Thiel and Gessner (75). The latter workers found that different methods

of preparation and treatment of nickel sulfide precipitates lead to products which differ immensely as to the extent to which they are attacked by hydrochloric acid. Thiel and Gessner were led to postulate the existence of different "modifications" of nickel sulfide roughly designated as the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -forms, corresponding to more or less definite solubilities in hydrochloric acid of a given strength. They advanced the belief that the different preparations differed in the extent of polymerization and that differences in solubility were to be attributed to this condition. Considering a given nickel sulfide preparation Thiel and Gessner designated as the  $\alpha$ -modification that portion which was quickly and easily soluble in cold 2 *N* hydrochloric acid, this form actually being soluble in 0.01 *N* acid. After removal of the  $\alpha$ -NiS by this treatment a more or less stationary state was reached, as measured by the concentration of dissolved nickel realized by further extraction with cold 2 *N* acid. Upon treatment with hot 2 *N* hydrochloric acid, however, another portion of the precipitate was rather easily and quickly removed until again a stationary state was obtained. The portion thus removed, being easily soluble in hot 2 *N* acid, was designated as  $\beta$ -NiS and the remainder, which could be readily dissolved only by the addition of an oxidizing agent, was characterized as  $\gamma$ -NiS. Apparently conversion of the more soluble preparations to the less soluble condition may readily be brought about. The solubility of precipitated nickel sulfide decreases markedly merely on standing in contact with acid solution. In pure water the effect is less. Higher temperatures seem to hasten the transition.

In addition to a growth of the crystals, the latter upon aging may be transformed to a different crystalline modification. In the case of zinc sulfide two different crystal forms are known to exist in nature. The regular form, or zinc blende, is by far the more abundant and is the stable form at ordinary temperatures, passing to the hexagonal or wurtzite form at or above the conversion point of 1020°C. (value given by Allen and Crenshaw (2a)). The solubility of wurtzite is given by Gmelin (27) as being about 4.3 times that of zinc blende. Wyckoff (84) gives the lattice constant of the zinc blende form as being 5.43 A.U. The values reported in the literature show some deviation from this figure, ranging from  $5.395 \pm 0.005$  (18, 25) to  $5.437 \pm 0.004$  (53). This disagreement may be due to small amounts of impurities such as iron sulfide in the natural specimens chosen for the various investigations.

Levi and Fontana (54) investigated four zinc sulfide precipitates prepared similarly to the series previously listed in reference to Krokowski's work. Their aim was to determine the crystal form of such precipitates, using the powder method of x-ray analysis, and also to examine the precipitates for the dimensions of the granules. They found that the pre-

precipitates all had the blende structure and that the granules of the four preparations had practically identical dimensions (about 20 A.U.). On the basis of their results Levi and Fontana make the statement that the differing behavior of zinc sulfide precipitates must be due to differences in states of agglomeration rather than to differences in crystal form or particle size. To be complete the statement should be further augmented by a definition of what is meant by "state of agglomeration."

The question as to whether zinc sulfide precipitates entirely in the blende form from acid solution under the action of hydrogen sulfide does not seem to be entirely settled. It is generally accepted that only the more stable blende form is precipitated from alkaline solution (2a, 81). As mentioned above, Levi and Fontana found only the blende form to be precipitated from solutions of the sulfate and acetate. Since it is not easy to distinguish between crystals of the zinc blende and zinc oxide type by x-ray methods, a small amount of the wurtzite form might easily have escaped detection. Allen, Crenshaw, and Merwin (2a) found by microscopic examination of crystals formed in sealed tubes in the presence of the supernatant liquid at temperatures between 200°C. and 400°C. that from acid solution both wurtzite and zinc blende forms were produced. From their investigations concerning the sulfides of zinc, iron, cadmium, and mercury they drew the general conclusion that the higher the temperature the greater the quantity of stable form produced, while the higher the acidity of the solution from which precipitation takes place, the greater the quantity of the unstable form. The acid concentration required to give pure marcasite or wurtzite (unstable forms of  $\text{FeS}_2$  and  $\text{ZnS}$ , respectively, at ordinary temperatures) falls with the temperature, being close to neutrality for marcasite at ordinary temperatures. They conjecture that the same statement probably holds for wurtzite (2b). This latter supposition as regards the formation of wurtzite is supported, however, neither by the work of Levi and Fontana (54) nor by the work conducted by the present authors. We found that a precipitate of zinc sulfide formed and aged in a solution 0.4 *N* in sulfuric acid and saturated with hydrogen sulfide consisted, according to x-ray analysis, mainly of crystals of the blende structure, though some indication was afforded by microscopic examination that the wurtzite form was also present to an extent roughly estimated to be in the neighborhood of 1 per cent. The microscopic examination cannot, however, be considered as conclusive evidence. In spite of the confusion in the literature regarding the question, it seems to be indicated by a review of the investigations carried out that in precipitation from acid solution the obtainment of both modifications of zinc sulfide is possible, and it may be said with equal justification that the form assumed under ordinary laboratory conditions is predominantly that of zinc blende.

Mellor (57a) lists four different forms in which mercuric sulfide may exist. Three of these are crystalline, while black amorphous mercuric sulfide is given as the fourth form. Of the three crystalline forms reported, the existence of two, namely  $\alpha$ -HgS or ordinary red cinnabar and  $\alpha'$ -HgS or black metacinnabarite, is unquestioned; they have been known for a long time to exist in nature. Cinnabar, having a trigonal structure, is the most commonly occurring natural form and is the most stable modification at ordinary temperatures, while the cubical (zinc blende type) structure of black metacinnabarite is the form usually assumed by mercuric sulfide precipitated from acid solutions of mercuric salts with hydrogen sulfide. The statement is made by Allen and Crenshaw (2a) that cinnabar is the stable modification at all temperatures up to the sublimation temperature ( $580^{\circ}\text{C}.$ ), but the later work of Rinse (61) tends to refute this. From vapor pressure data the latter finds that a transition point is indicated at  $386 \pm 2^{\circ}\text{C}.$ , above which temperature the black form is the stable modification. The third crystalline form listed by Mellor is the supposed new form reported by Allen and Crenshaw (2a), which is also a red hexagonal form but differing from ordinary cinnabar and not found in nature. Allen and Crenshaw based their report of the existence of this modification on evidence gained by microscopic examination. Kolkmeijer, Bijvoet, and Karssen (43), employing the powder method of x-ray investigation, found none of the preparations of mercuric sulfide described by Allen and Crenshaw to contain crystals different from the ordinary black and red forms.

The structure of red, trigonal cinnabar has been determined by Mauguin (57), using the Bragg method of x-ray analysis by which the dimensions of the unit cell were determined to be:  $a = b = 4.15 \text{ A.U.}$ ,  $c = 9.51 \text{ A.U.}$  It was found that with a slight deviation the particles were arranged on a rhombohedral lattice. The work was later confirmed by Kolkmeijer (43) and coworkers, using the powder method of x-ray analysis.

The structure and properties of natural and artificial black metacinnabarite have been investigated by various workers (31, 43, 53). There is entire agreement that the black form usually precipitated from acid solution is identical in structure with that of naturally occurring metacinnabarite, the atoms of mercury and sulfur being arranged on a face-centered cubic lattice of the zinc blende type. The edge of the unit cell is reported by Wyckoff (84) to be  $5.84 \text{ A.U.}$ , this value being in good agreement with the work of various investigators, including our own. The diffraction patterns of the black and red modifications of mercuric sulfide show striking agreement, in that the lines appearing on a pattern produced with metacinnabar also appear in the case of the trigonal modification. There are, however, many more lines obtainable in the latter case. This similar-

ity in certain line positions is attributed by Kolkmeijer, Bijvoet, and Karsen (42) to the complete equality of dimensions in the octahedral and basal planes of the two respective modifications

$$\left( \frac{a_{\text{black}}}{\sqrt{2}} = 4.14 \text{ A.U.} = a_{\text{red}} \right)$$

Böhm and Niclassen (10) report that mercuric sulfide precipitated at 0°C. gives at once a sharp interference pattern. In our work it was found that, while under the conditions of radiography used the fresh precipitate gave no sharp interference maxima, yet the period of aging necessary for the precipitate to assume a condition making possible a clear pattern was rather short. Apparently freshly precipitated mercuric sulfide which is rapidly formed tends to be of a more crystalline nature than a correspondingly "fresh" precipitate of zinc sulfide, which is formed relatively slowly from acid solution. An explanation of this rather surprising observation undoubtedly involves consideration of the relative magnitudes of orientation and agglomeration velocities (in the sense of Haber (30)) attendant to the formation of the respective precipitates. It may be experimentally shown that the crystallization velocity of zinc sulfide is relatively very small.

Since the red, cinnabarite form of mercuric sulfide is the more stable at ordinary temperatures it is to be expected that it will be formed upon aging of the black precipitate. Actually the observation has been generally made that the red modification is readily formed by digestion of the black gel with soluble alkali sulfides. Weiser (81) expresses the opinion that this process consists in the solution of the black form with subsequent precipitation of the less soluble, red hexagonal form. There is no definite proof, however, that such a mechanism is the actual case. According to Allen and Crenshaw, black "amorphous" mercuric sulfide is always formed first by the action of alkali sulfides on mercuric salts, but cinnabar only is obtained when the precipitate is digested with alkaline solution. Furthermore they report that cinnabar is formed from the other modification by application of heat alone or by heating the precipitate with 30 per cent sulfuric acid solution (2a). Our own experiments have shown that alkalinity is not a necessary condition for the formation of the red form, but the transformation occurs upon aging in the supernatant liquid at room temperature even in quite strongly acid medium. However, if the sulfide is precipitated from a neutral solution of the perchlorate and allowed to age in the resulting supernatant liquid saturated with hydrogen sulfide, transformation to the trigonal form, as indicated by the change in color of the precipitate, may be detected within a few hours and is appar-

ently complete within a day or two, whereas in more strongly acid the change is much retarded, a week or so being necessary for the change to become apparent at an acidity of 2 or 3 *N* in sulfuric acid. Proof of this transformation and the identity of the crystal forms involved was obtained by x-ray methods as well as by visual observation of the color changes taking place (59). If aging is conducted at higher temperatures (70°C.) the transformation is much accelerated, being complete within an hour or so in case the only acid present is that formed by the precipitation reaction, and if ammonia has also been added to the supernatant liquid (ammonium sulfide formed), the time necessary for complete conversion is further reduced to a matter of ten minutes or so. Transformation in case the precipitate was suspended in pure water or in dilute ammonium hydroxide was not detected. From these observations it appears that conversion from the cubic to the hexagonal form is promoted by low hydrogen-ion concentration, high concentration of hydrogen sulfide (or sulfide ion), and by higher temperatures, at least within a moderate range, of the supernatant liquid in which aging takes place. The presence of certain substances in solution, such as potassium iodide and sodium acetate, was found to retard the transformation, as did likewise the presence of post-precipitated zinc sulfide.

Evidence of the reverse change, namely from the red to the black form, does not seem to have been observed with the same degree of certainty. Observations have been reported by Allen and Crenshaw (2a), Spring (73), and Rinse (61), which indicate that heating the red precipitate may result in the formation of a black product which reassumes a red color if cooled slowly, but which remains black if cooled rapidly after being heated to a sufficiently high temperature. Assuming that the black color denotes the presence of the metacinnabarite form, these results support Rinse's conclusion that the regular modification is stable above 386°C. and are not in agreement with the statement made by Allen and Crenshaw to the effect that cinnabar is the stable form at all temperatures up to the sublimation point of 580°C. Roloff (63) concluded that the red sulfide changed to black through the action of light. The change depended on the presence of moisture, taking place more rapidly in alkaline medium than in pure water. No change took place in acid medium.

Proof that in the above-observed instances there is an actual change from the hexagonal to the cubic modification rests on the assumption that the respective colors are uniquely characteristic of the crystal forms. Milligan (58) found that either  $\beta$ -CdS (cubic) or  $\alpha$ -CdS (hexagonal) may be yellow or red, depending on the physical character of the precipitate. Likewise in the case of mercuric sulfide a difference in color may not necessarily signify a change in crystal modification.

Freshly precipitated cadmium sulfide has been shown (10, 58, 78) to exist as the above-mentioned two modifications, depending on the method of preparation. Milligan (58), investigating this observation more in detail, found that the  $\beta$ -CdS tends to be precipitated from cadmium sulfate solutions and under some conditions from the nitrate solutions, especially if the latter are hot and distinctly acid in reaction. The  $\alpha$ -CdS tends to be formed from the chloride, bromide, and iodide solutions, but these precipitates may also contain some of the  $\beta$ -modification. The formation of two different crystal modifications is thus indicated, and the possibility of transformation of one form to the other on aging is evident.

Again in the case of manganese sulfide, Schnaase (68) reports the identification by x-ray methods of three different crystal modifications. The green sulfide designated as  $\alpha$ -MnS, having a cubic, sodium chloride structure, is the stable modification. The red sulfide may consist of two different crystal forms designated as the  $\beta$ -modifications. One of these, the  $\beta$ -cubic form, has a cubic, zinc blende type of structure, while the other, the  $\beta$ -hexagonal modification, is of the wurtzite type. The identity of the crystal form assumed by a precipitate of manganese sulfide is again found to be dependent upon the method of preparation. Under conditions leading to the formation of the red sulfide it was concluded by Schnaase that the  $\beta$ -cubic and  $\beta$ -hexagonal modifications are simultaneously formed and hence always appear together in the precipitate. Predominance of one or the other depends again on the method of preparation. The  $\beta$ -cubic form predominates if a strong alkali sulfide such as sodium sulfide is used as the precipitating agent, while the  $\beta$ -hexagonal form occurs in the greater proportion if precipitation is effected by ammonium sulfide. All precipitates are, however, converted to the crystal form characteristic of the green sulfide after shorter or longer periods of time, at low or high temperatures, and in the dry or wet condition. The reverse process, namely the formation of the red form from the green, has never been observed (68).

#### THE AGING OF A MIXTURE OF METAL SULFIDES

When the precipitation of a metal sulfide takes place in the presence of another freshly formed metal sulfide and the resulting "mixed" precipitate is subjected to an aging process in the supernatant liquid, a mixed crystal formation may occur, the extent of which is dependent upon the similarity in size and shape of the ionic domains in the respective crystal lattices. Referring again to the case of the sulfides of mercury and zinc, it has been previously mentioned that both substances when precipitated from acid medium consist of submicroscopic crystals having the zinc blende type of lattice. The lattice constants of mercuric and zinc sulfides may be taken as 5.84 and 5.40 A.U., respectively.



In connection with their work with alkali halides, Havighurst, Mack, and Blake (32) state the rule that, if two substances have similar crystal structures, complete miscibility is possible if the difference in lengths of the cube edges is less than 5 per cent of the average value of the respective lattice constants: i.e.

$$\delta - \frac{a_1 - a_2}{1/2(a_1 + a_2)} < 0.05$$

However, partial miscibility may exist for values of  $\delta$  up to as high as about 0.10. It seems possible that these limits may vary with the kind of ions or atoms present. Barth and Lunde (5) found that complete miscibility is possible in the case of the halides of certain heavy metals ( $\text{Cu}^{\text{I}}$ , Ag, and Tl), even though the difference in lattice constants may be considerably greater than the limits set by Havighurst and coworkers for the case of the alkali halides. Considering the cubic modifications of the sulfides of zinc and mercury, we find that  $\delta$  has a value equal to 0.078. From this we should expect that at least a limited mixed crystal formation is possible.

The manner in which the lattice constant of the solvent will be affected by the presence of the solute atoms (or ions or molecules) may be quantitatively predicted in certain cases. Havighurst and coworkers (32) reason that solid solution may take place in two different ways:

1. Interstitial type. The solute atoms are crammed in between the solvent atoms and as a result always cause an enlargement of the unit cell regardless of the size of the solute atoms. Only partial miscibility can exist in such cases. The solute and solvent atoms need not be alike either chemically or in regard to their size and shape. The system C-Fe is considered an example of such a solid solution. No case has been recorded of interstitial solution in the case of salts, and it may be assumed that these considerations do not apply to systems of metal sulfides.

2. Substitutional type. In this case it is assumed that there is a more or less regular substitution in the space lattice of the solvent atoms by the solute atoms (or ions). At least in the case of salts the prerequisites as to chemical similarity and approximate equality in size and shape of the ionic domains must be fulfilled before solid solution of this type may take place. The assumption is made that the change in lattice parameters is a continuous function of the concentration of the solute. In the case of wholly miscible systems, at least, the relationship has been found to be practically linear, but exceptions to this might be expected to occur in systems of two salts with a common ion, wherein the dissimilarity in ionic domains is such as to make the components only partially miscible in each

other (32). This latter consideration may be of significance in regard to the system ZnS-HgS. From their work with alkali and ammonium halides Havighurst, Mack, and Blake formulated the following quantitative expression for this general rule of additivity as applicable to systems crystallizing in the cubic system

$$a^n = (a_2^n - a_1^n)x + a_1^n$$

where  $a$  is the lattice constant of the solid solution,  $a_2$  and  $a_1$  are the respective lattice constants of the components, and  $x$  is the mole fraction of the component having the lattice constant  $a_2$ . Values for  $n$  of 1 (79), 3, and 8 (28) have been suggested, but the above-named authors found a value of 1 or 3 to be most consistent with their results.

Substituting the known values of the lattice constants of zinc blende and metacinnabar and the lattice constant experimentally determined by the authors (59) for a precipitate obtained by the action of hydrogen sulfide on a solution containing both zinc and mercuric salts (5.79 A.U.) in the above equation we find a value of about 0.12 for the mole fraction of zinc sulfide present in the mixed crystal. The possibility must be kept in mind, however, that, owing to the large difference in the size of ionic domains found in this case, there may be strains set up in the lattice which might partially controvert the law of additivity.

The question as to how the atoms of the respective components are distributed in a mixed crystal seems still to be an open one. Among others, the view was taken by Tamman (74) that the atoms (or ions) of solute are regularly distributed throughout the solvent lattice. Laue (52), on the other hand, from consideration of x-ray diffraction phenomena asserts that the solute atoms (or ions) must be distributed in an entirely random fashion. He points out that were regular distribution in the sense of Tamman the case, there would be a regular periodicity in the lattice which should give rise to new, weak interference lines on the diffraction diagram. Neither Vegard (79), nor Havighurst, Mack, and Blake (32), investigating mixed crystals in systems of the alkali and ammonium halides, nor Barth and Lunde (5), working with the halides of copper, silver, and thallium, were able to detect any such periodicity required by Tamman's assumption. As pointed out by Davey (17), such lines have never been found in the case of a mixed crystal, although they have been found in the case of certain systems such as (a) 0.25 mole Si and 0.75 mole Fe (corresponding to the possible compound  $\text{Fe}_3\text{Si}$ ) and (b) 0.50 mole Pd and 0.50 mole Cu ( $\text{PdCu}$ ), and others where likewise a chemical compound is indicated. From these considerations Davey concludes that uniform distribution of the components of a solid solution is evidence of a definite chemical compound, and

that the ions of the same sign in a mixed crystal are arranged in an entirely random fashion.

In regard to the proof of the existence of solid solution or mixed crystal formation by x-ray methods, caution should be used in the interpretation of results. In dealing with systems of two components we may have a single phase corresponding to complete solubility of one component in the other, or we may have two phases corresponding either to total immiscibility or to limited miscibility. In case two solid phases are present and both are composed of crystals of appropriate size and of random orientation, it is usually easy to demonstrate their existence by obtaining at a single exposure two diffraction patterns, one from each of the solid phases. If the crystals of one of the phases are very small or very imperfect, the diffraction pattern due to their presence may be composed of only a few very broad and indistinct lines. In such an event the presence of a second phase may easily escape detection by x-ray methods. If solution has taken place the diffraction pattern of the particular phase in question should resemble that of the pure solvent with the lines somewhat displaced, corresponding to an increase or decrease in the lattice constant. Davey (17) points out that a change in the lattice constant, although always found in solid solutions when the concentration of the solute is sufficiently great, is not basic evidence of solid solution or mixed crystal formation. However, it is an indication of such a phenomenon which is well supported by theory. The fallacy of assuming complete solubility of one component in the other solely on the basis that only a single diffraction pattern is obtained is evident. The possibility must always be considered that a second phase may actually be present and that under more favorable conditions its existence could be demonstrated. Also, it should be born in mind that a second phase, though present, may not be in such a condition as to give a distinguishable diffraction pattern. These considerations are especially pertinent to the system mercuric sulfide-zinc sulfide. Only a single diffraction pattern was obtained from each of two precipitates containing 48 and 39 mole per cent of zinc sulfide, respectively. The lattice constants found for the precipitates were identical within experimental error. The diffraction pattern obtained was similar to that of pure mercuric sulfide. The degree of alteration of the lattice constant indicated, however, that the mixed crystal contained zinc sulfide only to the extent of about 12 mole per cent. To account for the remainder of the zinc sulfide present in the precipitate there are two possibilities open. Either there is a second phase consisting of pure zinc sulfide, or one consisting of a solid solution of mercuric sulfide in zinc sulfide. The latter possibility represents a case in which we have two solid phases, each of which is a mixed crystal, mercuric sulfide being the predominant component of one and hence the solvent,

while zinc sulfide is the solvent in the second phase. It is a general rule that if A dissolves in B then B dissolves in A, but the degree of solubility of A in B is no criterion of the degree of solubility of B in A. Allowing for the possibility of such a second phase in which zinc sulfide is the solvent, the concentration of mercuric sulfide in that phase may be very low. In any event, whether the second phase consisted of pure zinc sulfide or a mixed crystal of mercuric sulfide in zinc sulfide, the condition of the crystals was such as to allow no diffraction pattern to be obtained from that phase. A precipitate consisting of 21 mole per cent mercuric sulfide which had been aged three days gave a diffraction pattern so indistinct and of so few lines that it was uninterpretable. The diffraction pattern obtained with a precipitate produced by the long time action (one month) of hydrogen sulfide on a 2 *N* sulfuric acid solution originally containing salts of both zinc and mercury contained two very weak lines which could not be explained on the assumption of a single solid phase consisting of a mixed crystal of zinc sulfide in mercuric sulfide. Excluding these two lines from consideration it was found that the pattern obtained from this precipitate which contained 39 mole per cent zinc sulfide could be interpreted according to such an assumption and led to a value for the lattice constant of 5.79 A.U. The presence of the two lines is indicative of a second solid phase, but because of their indefinite character it is impossible to say whether they may have been due to the presence of pure zinc sulfide or to a second type of mixed crystal, the possibility of which has been discussed.

In connection with the above, mention may be made of the mineral guadalcazarite—(Hg, Zn) (S, Se), 10 mole per cent ZnS—which has been investigated by Hartwig (31), and found by him to be isomorphous with metacinnabarite and zinc blende and to have a lattice constant of  $5.781 \pm 0.006$  A.U. It is to be noted that this naturally occurring mineral has an apparent lattice constant nearly identical with the synthetic product described above. Moreover, its composition is about that indicated by our researches as corresponding to the mixed crystal present in the precipitate obtained by the long time aging of a mixture of mercuric and zinc sulfides precipitated from acid medium in the presence of an excess of hydrogen sulfide.

Analogous to the presumed existence of mixed crystals in the case of the sulfides of mercury and zinc is the previously mentioned case of mixed crystal formation in the cases of Mn–Cd sulfides and Mn–Zn sulfides as reported by Schnaase (68). All three of these sulfides may assume both the zinc blende and the wurtzite structure. The respective lattice constants for the zinc blende forms of zinc sulfide, manganous sulfide, and cadmium sulfide may be taken as 5.40 A.U., 5.60 A.U., and 5.82 A.U. It may be inferred from this that conditions for mixed crystal formation

in the case of the pairs mentioned fulfill the requirements previously cited. From the work of Böttger and Druschke (11) and of Ahrens (1) there is evidence that in the case of mercuric sulfide and cadmium sulfide mixed crystals are formed on aging the mixed precipitate. Owing to the close similarity of lattice constants of these two respective sulfides, proof of the phenomenon by x-ray methods is practically impossible.

It may be mentioned here, in connection with the above, that it is extremely difficult if not impossible to extract completely the zinc from the (Hg-Zn)S "mixed" precipitates with dilute hydrochloric acid. This at least shows that the zinc sulfide is intimately associated with the mercuric sulfide. Likewise Böttger and Druschke and Ahrens encountered the same effect in the (Hg-Cd)S "mixed" precipitate.

#### POSTPRECIPITATION OF ZINC SULFIDE WITH MERCURIC SULFIDE AND COPPER SULFIDE, RESPECTIVELY

In connection with the general discussion of postprecipitation given in a previous chapter of this paper, it is of interest to consider some of the phenomena in a more detailed manner. The system CuS-ZnS was studied by Kolthoff and Pearson (46) and that of HgS-ZnS by Kolthoff and Moltzau (59). In both cases it could be shown that the adsorbed hydrogen sulfide was mainly responsible for the occurrence of postprecipitation of zinc sulfide. Thus an inhibition of the effect was observed on partly replacing the hydrogen sulfide adsorbed on the surface of the copper sulfide or mercuric sulfide by organic substances containing polar sulfur groups. Cysteine was found to be especially effective.

In general, it was found that the amount of zinc sulfide postprecipitated in a given time decreases with increasing acidity. For the same acid normality less postprecipitation was observed with hydrochloric than with sulfuric acid, since the activity of the hydrogen ions in hydrochloric acid solution is greater than that in sulfuric acid solution of the same normality.

In the presence of copper sulfide obtained by hot precipitation or by aging at room temperatures, more zinc sulfide is precipitated than in the presence of a fresh precipitate of copper sulfide obtained by cold precipitation from sulfuric acid medium. Aged precipitates of copper sulfide obtained by either hot or cold precipitation have practically the same promoting effect on the precipitation of zinc sulfide. The promoting effect of such aged precipitates is much greater than that of the fresh precipitate of copper sulfide obtained by precipitation in the cold, but less than that of the precipitate freshly prepared from hot solution. The method of preparation of the copper sulfide, i.e., whether from neutral or acid solution, has also been shown to be of influence in the promotion of precipitation of

zinc sulfide. These effects are thought to involve changes in the extent of surface of copper sulfide on aging.

When postprecipitation of zinc sulfide is brought about through the presence of freshly precipitated mercuric sulfide the resulting "mixed" precipitate, though apparently quite as black as pure mercuric sulfide, is more slimy and much more difficult to filter. Upon aging of the mercuric sulfide precipitate a marked decrease in its ability to promote the precipitation of zinc sulfide is to be observed. Precipitates aged at room temperature, whether precipitated from hot or cold solution, exhibit the same promoting ability. A certain "aged" condition of a mercuric sulfide precipitate is probably reached more quickly at higher than at lower temperatures, owing partially, at least, to an increased tendency towards transformation to the trigonal form at higher temperatures. Mercuric sulfide aged in acid solutions exhibits a slightly greater promoting action on the precipitation of zinc sulfide than that aged in more nearly neutral medium. This again is undoubtedly related to an increased tendency to assume the cinnabar structure at low hydrogen-ion concentration.

In studying the effect of acidity on the postprecipitation of zinc sulfide with mercuric sulfide it was found that at higher acidities the amount of zinc sulfide entering the precipitate in a given time falls off much more slowly with increasing acidity than is to be expected on the basis of solubility principles, while at lower acidities this abnormality is not as pronounced. Employing freshly precipitated mercuric sulfide it was found that an appreciable quantity of zinc, its magnitude depending upon the acidity, enters the solid phase within the first thirty minutes or so after saturation with hydrogen sulfide, and that thereafter precipitation of zinc sulfide takes place much more slowly until a point corresponding to the solubility of well-aged zinc sulfide is reached. At lower acidities the presence of a very small amount of mercuric sulfide will lead to the precipitation of relatively large amounts of zinc sulfide within a period of time of such length that no precipitate would be obtained from a solution of a zinc salt alone. At higher acidities (2 *N* in sulfuric acid) the amount of zinc sulfide entering the precipitate in a given, relatively short time of shaking closely approximates a direct proportionality with the amount of fresh mercuric sulfide present. Keeping constant the acidity and the amount of mercuric sulfide present, and varying the original concentration of zinc in solution, it was indicated that the amount of zinc carried down from solution was more or less directly proportional over a limited range to the concentration of zinc salt in solution.

These results were interpreted as clearly indicating that the process by which zinc sulfide appears in the precipitate under the promoting action of mercuric sulfide at acidities where it alone would not precipitate (at least

not in the same time) involves an adsorption phenomenon as well as precipitation of zinc sulfide in the ordinary sense. During the initial period of precipitation adsorption is the primary process to be considered and is mainly responsible for the appearance of zinc sulfide in the precipitate during that period, although precipitation in the ordinary sense also occurs to account for the slower but continued disappearance of zinc ions from solution. At higher acidities, where the rate of true precipitation is relatively slow, the rôle played by adsorption is emphasized, as evidenced by the experimental results reviewed above, while at lower acidities true precipitation takes place so rapidly and to such an extent that the adsorption effect is largely overshadowed. This adsorption process involves an exchange mechanism whereby the zinc ions replace the hydrogen of the hydrogen sulfide adsorbed on the surface of the mercuric sulfide. It has been shown experimentally by shaking a well-washed, freshly prepared precipitate of mercuric sulfide with a neutral solution of zinc sulfate, under which condition the hydrogen sulfide is retained by the mercuric sulfide in an adsorbed state, that an appreciable quantity of zinc ions leaves the solution and is replaced by an equivalent amount of hydrogen ions. The presence of other substances, such as strychnine or aluminum ions, which also act as counter ions on the surface of the mercuric sulfide, leads to a decrease in the adsorption of zinc ions. Likewise the presence of strychnine in acid solution saturated with hydrogen sulfide inhibits the "carrying down" of zinc sulfide by mercuric sulfide.

The greater tendency to ionize exhibited by the adsorbed hydrogen sulfide over that exhibited by the hydrogen sulfide present in the bulk of the solution is cited as an explanation of the increased reactivity of zinc ions to form zinc sulfide at the surface of the mercuric sulfides. According to the theory advanced there is a competition between hydrogen ions and zinc ions for adsorption as counter ions. Increasing the ratio of zinc-ion concentration to hydrogen-ion concentration twofold would make conditions twice as favorable for adsorption of zinc ions. This consideration readily affords an explanation of the decrease in adsorption effect with acidity and of the observation that at a given high acidity the amount of zinc ion disappearing from solution is more or less proportional to the concentration of zinc in solution.

In this paper emphasis has been placed upon the fact that in the cases of  $\text{CuS-ZnS}$  (46) and  $\text{HgS-ZnS}$  (59) we are dealing with a postprecipitation effect. Work now being done in this laboratory by Mr. Griffith shows that the same type of phenomenon is exhibited by the sulfides of bismuth and zinc. It is not, however, to be inferred from the foregoing discussion that the presence of a sulfide of the third group in a sulfide precipitate of the second group is always to be attributed to a postprecipitation effect.

It may be possible to find cases of definite coprecipitation, although they have not so far been observed in work done in this laboratory.

It is planned to make a more exhaustive and systematic study of the entire field.

## REFERENCES

- (1) AHRENS, W.: Dissertation, Leipzig, 1933.
- (2) (a) ALLEN, E. T., CRENSHAW, J. L., AND MERWIN, H. E.: *Z. anorg. Chem.* **79**, 125 (1913).
- (b) *Ibid.* **90**, 107 (1915).
- (3) AUGER, M., AND ODINOT, L.: *Compt. rend.* **178**, 710 (1923).
- (4) BALAREW, D.: *Z. anorg. allgem. Chem.* **165**, 192 (1927); *Kolloidchem. Beihefte* **30**, 249 (1930). The latter gives a complete review of Balarew's work on inner adsorption.
- (5) BARTH, T., AND LUNDE, G.: *Z. physik. Chem.* **122**, 293 (1926).
- (6) BASSETT, H.: Fourth Report on Colloid Chemistry, British Association for the Advancement of Science, p. 5 (1922).
- (7) BAUBIGNY, H.: *Compt. rend.* **94**, 1183, 1251, 1473, 1595 (1882); **95**, 34 (1883); **105**, 751, 805 (1888); **107**, 1148 (1888); **108**, 236, 450 (1889).
- (8) BERGLUND, E.: *Z. anal. Chem.* **22**, 184 (1883).
- (9) BERNFELD, I.: *Z. physik. Chem.* **25**, 46 (1898).
- (10) BÖHM, J., AND NICLASEN, H.: *Z. anorg. allgem. Chem.* **132**, 1 (1923).
- (11) BÖTTGER, W., AND DRUSCHKE, K.: *Ann.* **453**, 315 (1927).
- (12) BRUNER, L.: *J. Chem. Soc., Abstracts* **92**, (2), 349 (1907).
- (13) BRUNER, L., AND ZAWADSKY, J.: *Z. anorg. allgem. Chem.* **65**, 136 (1910); **67**, 454 (1910).
- (14) BRUNI, G., AND PADOA, M.: *J. Chem. Soc., Abstracts* **90**, (2), 157 (1906).
- (15) CALVERT: *J. prakt. Chem.* **71**, 155 (1857).
- (16) CRAIG, A.: *Chemist-Analyst* **21**, No. 3, 8 (1932).
- (17) DAVEY, W. P.: *A Study of Crystal Structure and its Applications*, pp. 524-40. McGraw-Hill Book Co., Inc., New York (1934).
- (18) DEJONG, W. F.: *Z. Krist.* **66**, 515 (1928).
- (19) FEIGL, F.: *Z. anal. Chem.* **65**, 25 (1924).
- (20) FEIGL, F.: *Z. anorg. allgem. Chem.* **157**, 269 (1926).
- (21) FEIGL, F.: *Qualitative Analyse mit Hilfe von Tüpfelreaktionen*, 2nd edition, pp. 63-74. Leipzig (1935).
- (22) FENIMORE, E. P., AND WAGNER, E. C.: *J. Am. Chem. Soc.* **53**, 2453 (1931).
- (23) FREUNDLICH, H., AND SCHUCHT, H.: *Z. physik. Chem.* **85**, 660 (1913).
- (24) FUNK, W.: *Z. anal. Chem.* **46**, 93 (1907).
- (25) GERLACH, W. VON: *Physik. Z.* **23**, 114 (1922).
- (26) GLIXELLI, S.: *Z. anorg. Chem.* **55**, 297 (1907).
- (27) GMELIN, L.: *Handbuch der anorganischen Chemie*, 8th edition, **32**, 201 (1924).
- (28) GRIMM, H. G., AND HERZFELD, K. F.: *Z. Physik* **16**, 84 (1923).
- (29) GRUNDMANN, R.: *J. prakt. Chem.* **73**, 241 (1858).
- (30) HABER, F.: *Ber.* **55**, 1717 (1922).
- (31) HARTWIG, W.: *Sitzber preuss. Akad. Wiss. Physik-math. Klasse*, p. 79 (1926).
- (32) HAVIGHURST, R. J., MACK, E., AND BLAKE, F. C.: *J. Am. Chem. Soc.* **47**, 29 (1925).
- (33) HAWLEY, L. F.: *J. Am. Chem. Soc.* **29**, 1011 (1907).



- (34) HERTZ, W.: *Z. anorg. Chem.* **27**, 390 (1901).
- (35) HILLEBRAND, W. F.: *J. Am. Chem. Soc.* **29**, 1019 (1907).
- (36) HILLEBRAND, W. F., AND LUNDELL, G. E. F.: *Applied Inorganic Analysis*, p. 170. John Wiley and Sons, New York (1929).
- (37) IMMERWAHR, CL.: *Z. Elektrochem.* **7**, 477 (1901).
- (38) JEFFREYS, C. E. P., AND SWIFT, E. H.: *J. Am. Chem. Soc.* **54**, 3219 (1932).
- (39) JELLINEK, K., AND CZERWINSKI, J.: *Z. physik. Chem.* **102**, 476 (1922).
- (40) KATO, H.: *Chem. Abstracts* **28**, 1951, 4332 (1934).
- (41) KLING, A., LASSIEUR, A., AND LASSIEUR, MME. A.: *Compt. rend.* **180**, 517 (1925).
- (42) KNOX, J.: *Z. Elektrochem.* **12**, 477 (1906).
- (43) KOLMEIJER, N. H., BIJVOET, J. M., AND KARSSSEN, A.: *Rec. trav. chim.* **43**, 678, 894 (1924).
- (44) KOLTHOFF, I. M.: *J. Phys. Chem.* **35**, 2711 (1931).
- (45) KOLTHOFF, I. M., AND DIJK, J. C. VAN: *Pharm. Weekblad* **59**, 1351 (1922).
- (46) KOLTHOFF, I. M., AND PEARSON, E. A.: *J. Phys. Chem.* **36**, 549 (1932).
- (47) KOLTHOFF, I. M., VON FISCHER, W., AND ROSENBLUM, C.: *J. Am. Chem. Soc.* **56**, 832 (1934).
- (48) KRISHNAMURTI, S.: *J. Chem. Soc.* **1926**, 1549.
- (49) KROKOWSKI, T.: *Roczniki Chem.* **13**, 561 (1933).
- (50) LARSEN, G.: *Z. anal. Chem.* **17**, 312 (1878).
- (51) LASSIEUR, A.: *Chimie & industrie*, Special No. 153, March (1932).
- (52) LAUE, M. VON: *Ann. Physik* **56**, 493 (1918).
- (53) LEHMAN, W. M.: *Z. Krist.* **60**, 379 (1924).
- (54) LEVI, G. R., AND FONTANA, C. G.: *Chem. Abstracts* **22**, 3851 (1928).
- (55) LUCAS, R.: *Z. anorg. Chem.* **41**, 193 (1904).
- (56) MANCHOT, W., GRASSL, G., AND SCHNEEBERGER, A.: *Z. anal. Chem.* **67**, 177 (1925).
- (57) MAUGUIN, C.: *Compt. rend.* **176**, 1483 (1923).
- (57a) MELLOR, J. W.: *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. IV, p. 944. Longmans, Green and Co., London (1923).
- (58) MILLIGAN, W. O.: *J. Phys. Chem.* **38**, 797 (1934).
- (59) MOLTZAU, D. R.: Thesis, University of Minnesota, 1935.
- (60) MOSER, L., AND BEHR, M.: *Z. anorg. allgem. Chem.* **134**, 49 (1924).
- (61) RINSE, J.: *Rec. trav. chim.* **47**, 28 (1928).
- (62) RIVOT AND BOUQUET: *J. prakt. Chem.* **54**, 203 (1851).
- (63) RLOFF, M.: *Z. physik. Chem.* **26**, 343 (1898).
- (64) ROSENBLADT, TH.: *Z. anal. Chem.* **26**, 15 (1887).
- (65) RUFF, O.: *Z. anorg. allgem. Chem.* **185**, 387 (1929).
- RUFF, O., AND ASCHER, E.: *ibid.* **185**, 369 (1929).
- (66) RUFF, O., AND HIRSCH, B.: *Z. anorg. Chem.* **151**, 81 (1926).
- (67) SCHAEFER: Dissertation, Leipzig, 1906.
- (68) SCHNAASE, H.: *Z. physik. Chem.* **20B**, 89 (1933).
- (69) SCHNEIDER, R.: *J. Chem. Soc., Abstracts* **27**, 228 (1874).
- (70) SMITH, G. M.: *J. Am. Chem. Soc.* **44**, 1500 (1922).
- (71) SMITH, G. M., AND SEMON, W. L.: *J. Am. Chem. Soc.* **46**, 1325 (1924).
- (72) SPIRGATUS, H.: *J. prakt. Chem.* **57**, 184 (1852).
- (73) SPRING, W.: *Z. anorg. Chem.* **7**, 382 (1894).
- (74) TAMMAN, G.: *Z. anorg. allgem. Chem.* **107**, 1 (1919).
- (75) THIEL, A., AND GESSNER, H.: *Z. anorg. allgem. Chem.* **86**, 1 (1914).
- (76) THIEL, A., AND OHL, H.: *Z. anorg. allgem. Chem.* **61**, 396 (1909).

- (77) TREADWELL, W. D., AND GUTTERMAN, K. S.: Z. anal. Chem. **52**, 459 (1913).
- (78) ULRICH, F., AND ZACHARIASEN, W.: Z. Krist. **62**, 260 (1925).
- (79) VEGARD, L.: Z. Physik **5**, 17 (1921).
- (80) WEIGEL, O.: Z. physik. Chem. **58**, 293 (1907).
- (81) WEISER, H. B.: The Colloidal Salts, pp. 83, 94. The McGraw-Hill Book Co., Inc., New York (1928).
- (82) WEISER, H. B., AND DURHAM, E. J.: J. Phys. Chem. **32**, 1061 (1928).
- (83) WORK, L. T., AND ODELL, I. H.: Ind. Eng. Chem. **25**, 543 (1933).
- (84) WYCKOFF, R. W. G.: The Structure of Crystals, 2nd edition, pp. 226, 229. The Chemical Catalog Co., Inc., New York (1931).



# THE FRIEDEL-CRAFTS SYNTHESSES

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## I. INTRODUCTION

In all of organic chemistry there are, perhaps, no reactions which have been so widely studied and still are so poorly understood as the Friedel-Crafts reactions. It is difficult to find other reactions which have been as generally applied in industry and in the laboratory as the Friedel-Crafts reactions, since they constitute one of the most generally applicable classes of reactions for the synthesis of all types of compounds.

The original Friedel-Crafts reaction has been extended, revised, and modified. A variety of condensing agents will introduce groups ranging from methyl, alkenyl, and phenyl to acyl groups of such varied nature as acetyl or nitro. Single atoms, such as sulfur, oxygen, arsenic, and phosphorus, may also be introduced into the benzene nucleus.

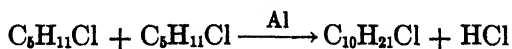
The mechanism of this reaction is not always clear. In many cases it appears to vary with the nature of the reactants, the condensing agent, and the solvent. Since the reaction has been applied with success to the alkylation and acylation of aliphatic substances, it seems reasonable to believe that there is no single class of compounds that will resist all types of Friedel-Crafts reactions if the proper conditions are selected. *Thus we prefer to think of a group of Friedel-Crafts reactions of which there are several types.*

#### A. Historical

The new interest injected into organic chemistry by Frankland's discovery of the organozinc compounds stimulated a series of studies on the action of various metals on alkyl halides, one of which resulted in the discovery of the Friedel-Crafts reaction. Historically, it is of interest to note that prior to the observations of Charles Friedel and James Crafts, which led to the discovery of the Friedel-Crafts reaction, several cases of alkylation and acylation of aromatic compounds by means of metals and metallic compounds had been reported.

In 1869, Zincke (467) reported the synthesis of diphenylmethane from benzyl chloride and zinc in benzene solution. In subsequent reports (468, 469, 470), up to the year 1872, Zincke reported similar syntheses. In 1873, Grucarevic and Merz (162) reported the acylation of aromatic types using acid halides in the presence of zinc dust (330). Doebner and Stackman (84a), in 1876, found that zinc oxide would introduce chloroform or phenyltrichloromethane into phenol to yield salicylaldehyde or *o*-benzoylphenol. It was pointed out in this latter report that zinc chloride was formed during the reaction. As Friedel and Crafts later showed (122), zinc chloride was the active condensing agent in all of these syntheses.

In 1877, Charles Friedel and James Crafts (119, 121) treated amyl chloride with thin aluminum strips. A reaction occurred with the formation of long chain alkyl halides and hydrocarbons. In seeking an explanation for this peculiar behavior, Friedel and Crafts suggested that the hydrogen of one amyl radical united with the halogen of another with the elimination of hydrogen chloride.

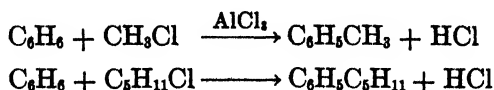


Thus, the first reported case of a Friedel-Crafts reaction was with an aliphatic compound. Yet this valuable class of aliphatic reactions was to remain undeveloped for over fifty years, while the mistaken concept prevailed that the Friedel-Crafts reaction was confined to aromatically bound hydrogen!

In these same studies, Friedel and Crafts found that the active substance

for catalyzing the reaction was aluminum chloride, formed by the union of the chlorine from the alkyl halides and the aluminum.

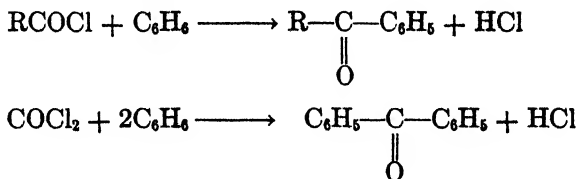
In benzene the reaction was observed to yield well-defined substances with alkyl halides. Short- or long-chained alkylbenzenes were obtained using benzene, aluminum chloride,<sup>1</sup> and alkyl halides. In every case hydrogen halide was eliminated.



Alkyl polyhalides were found to react (69) with the same ease to yield polyphenyl compounds.



In an analogous manner, it was found that ketones could be synthesized by this aluminum chloride condensation.



This latter reaction was shown not to yield anthraquinone (124a).

In these early papers, it was pointed out that halogenobenzenes would not react in the manner of alkyl halides (121), and that alkyl iodides were too unstable to be generally useful in this reaction (119). It was found that ethyl chlorocarbonate did not behave normally (121) as an acid halide; on the contrary, it decomposed in the reaction with benzene to yield as final products ethylbenzene, carbon dioxide, and hydrogen chloride.



Aluminum chloride was not the only efficient condensing agent (122). Ferrous chloride, ferric chloride, zinc chloride, and sodium aluminum chloride were found to be of value. It was further pointed out that only the anhydrous salts were suitable as condensing agents.

Thus, in a brief period of about six weeks Friedel and Crafts published three papers which laid the foundation and set the outline of the reaction named for these investigators (6).

<sup>1</sup> In order to simplify reactions,  $\text{AlCl}_3$  will be used throughout instead of  $\text{Al}_2\text{Cl}_6$ , as the formula for aluminum chloride.

### B. Definition and scope

At the present time it appears to be virtually impossible to define the Friedel-Crafts "reaction" so that the definition embraces a workable picture of the facts. The simple explanation that the Friedel-Crafts reactions introduce alkyl, aryl, and acyl groups into various classes of compounds in the presence of certain metal halides does not by any means truly represent the case. Yet the Friedel-Crafts reactions are generally used at the present time to introduce either alkyl or keto groups, although many of these reactions introduce highly specialized groups such as nitro, carboxyl, sulfo, hydroxyl, sulfonic, nitrilo, phenyl, and others. Apart from the aluminum chloride, the condensing agent may be, among others, ferric, stannic, boron, mercury, zinc, titanium, or antimony chlorides.

Essentially, the Friedel-Crafts "reaction" is an *activation reaction* (304). Either the hydrogen of the nucleus or a radical of the other reactant, or both, undergoes activation by the aluminum chloride. This means that the cases where activation is obtained essentially by metal halides should fall into the classes of *reactions* that are generally incorporated in and collectively known as the *Friedel-Crafts Reaction*. Thus the Gattermann, Gattermann-Koch, Hoesch-Houben, Fries, Scholl, polymerization, and cracking reactions would become subdivisions of the Friedel-Crafts reactions. While this is a fine picture of the facts, for the benefit of a reasonable clarity it is necessary to limit the sweeping embrace of the reactions.

To facilitate discussion, the reactions will be divided into alkylation and acylation. Under alkylation will be discussed all reactions that join carbon to carbon in such manner that the introduced carbon joined directly to the nucleus in the final product does not hold a doubly bound oxygen, a nitrogen-containing derivative of it, or a similar group. All other reactions are classed as acylations. There are indefinite borderline cases. However, this classification seems to be a reasonable division, although it fails to account for the catalysts, solvents, or other experimental conditions. It is understood that metal halides serve as the condensing agents.

Unfortunately, the exigencies of space demand limitation of the discussion to a superficial consideration of highly specialized cases of the use of metal halides in cracking, reduction, polymerization, or the Scholl reaction, although these fields are intimately concerned with the Friedel-Crafts syntheses.

It has not been possible to include *all* references or to include a complete discussion of the industrial applications of the reaction as revealed in part by the patent literature.

## II. ALKYLATION

As one of the most general of the Friedel-Crafts reactions, alkylation has become valuable for the synthesis of alkylated substances, principally

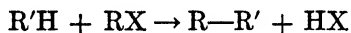
hydrocarbons of the aromatic series. The methods of introducing alkyl groups vary. The reactants may be of the most varied nature, as may also the nuclei undergoing substitution and the condensing agent, the solvent, and the conditions of reaction.

It is noteworthy that practically all of the unreliable Friedel-Crafts reaction types are reported in cases of alkylation. Generally, neither the configuration of the entering group nor the orientation in the nucleus can be accurately predicted in alkylation. In fact, alkylation appears to be of an entirely different nature as compared with acylation in respect to reliability, yields, or mechanism.

Unfortunately, in many cases the experimental facts have not warranted the generalizations made, and the *residual products* have been separated from the principal products and discarded. Thus the true nature of many reactions has remained obscure until comparatively recent years.

#### A. Aromatic compounds

1. *The reaction of alkyl halides.* The general reaction for the alkylation of aromatic compounds may be represented by the union of an alkyl radical of a halide with an aromatic nucleus with the elimination of hydrogen halide. Aluminum chloride may be used as a typical condensing agent.



where R and R' are alkyl and aryl groups, respectively.

Friedel and Crafts (119) showed that one of the simplest alkyl halides, methyl chloride, would react with benzene to yield toluene.

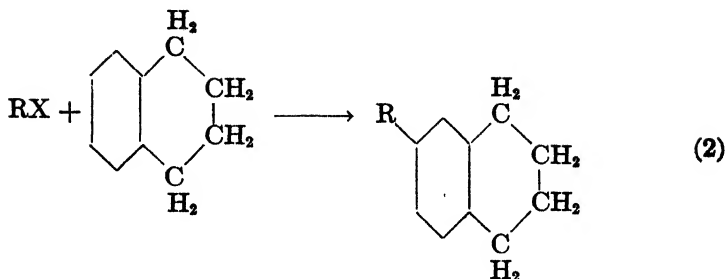
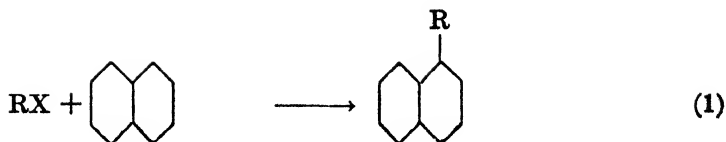


However, the reaction was found to be difficult to control and polymethylated benzenes, including xylene and hexamethylbenzene, also resulted. Jacobson (209) found that the yields of methylaryl compounds could be improved by introducing the methyl chloride under a slight pressure. Others (5) have observed that the methylation may be of a varied nature. That is, mono-, di-, tri-, tetra-, penta-, and hexa-methylbenzenes are all produced in the same reaction in varying proportions, depending on the conditions.

Ethyl halides have been observed to behave in a similar manner to yield mono- or poly-ethyl compounds (119, 446, 191, 192, 11).

The simple benzene nuclei are, of course, not the only types to undergo alkylation. Substituted nuclei, such as are present in phenols (163), aldehydes (144, 147), esters (144), and alkylbenzenes (15, 20, 119, 209), and the condensed aromatic rings, such as naphthalene (191, 192) or tetralin (11), undergo similar substitutions.





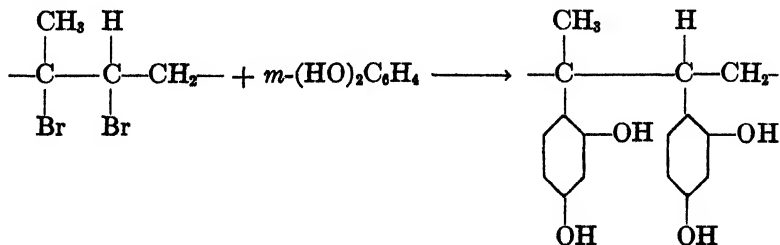
Reaction 1 gives  $\alpha$ -substitution, while reaction 2 appears to result in  $\beta$ -substitution exclusively.

Higher alkyl halides react similarly to the simple halides. Propyl (144, 446), butyl (167, 163, 20, 291a), and amyl (119, 144) halides react to yield, largely, branched alkyl substances. Generally, regardless of the configuration of the alkyl halide, the final product contains an alkyl group of the highest possible branching (144). (See the discussion of orientation and reliability, on p. 367.)



The alkyl polyhalides also react as predicted to yield progressively phenylated compounds (42). Carbon tetrachloride yields aryltrichloromethane, diaryldichloromethane, and triaryldichloromethane. The fourth chlorine atom is not replaced by a phenyl radical (42, 121, 191, 192). The reaction is easily controllable.

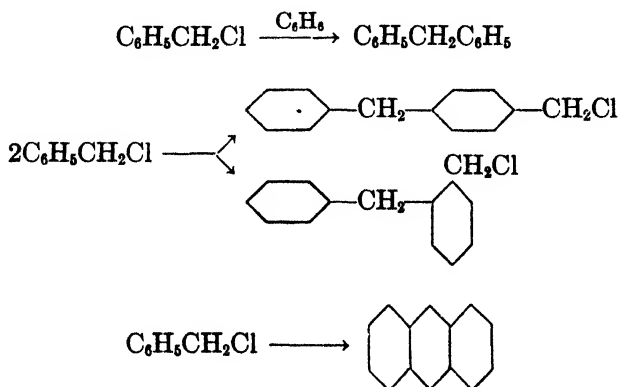
The very high molecular weight alkyl halides behave as the simpler one (93). Rubber dibromide (141), for example, will alkylate certain substituted benzenes, such as the mono- and poly-phenols, the cresols, anisole, or phenetole. The condensing agent may be either ferric or aluminum chloride.



Guttapercha dibromide behaves in a similar manner (141).

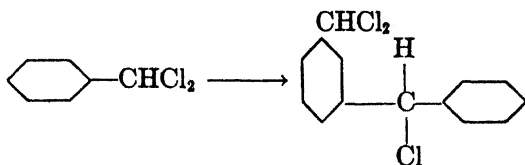
Chloropicrin yields with benzene (28) triphenylcarbinol and triphenylmethane. The hydroxyl and hydrogen attached to the methane carbon atoms, respectively, apparently arise from the hydrolysis of the reaction complex in the course of working up the products.

Alkyl halides containing aromatic nuclei react easily with various nuclei to yield substituted products. Benzyl chloride will react with benzene (467, 470, 237, 404) to form diphenylmethane. Benzyl chloride was observed to react with itself to form anthracene (237) and substituted benzyl chlorides (445).

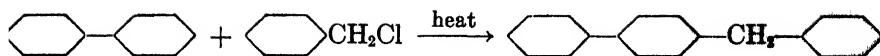


This last reaction probably takes place in two stages. The dihydroanthracene first formed is dehydrogenated to yield anthracene (383).

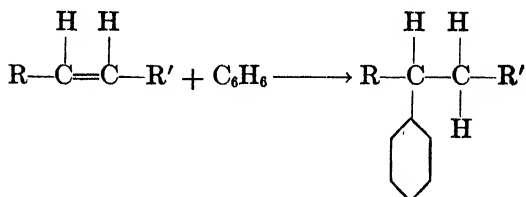
The phenylalkyl dihalides behave in a similar manner (445) to yield a small quantity of meta-substituted products.



It is of significance that diphenylmethyl bromide and phenol (51) or benzyl chloride with diphenyl, benzene, toluene, *o*-xylene, or mesitylene will yield, at elevated temperatures *without a catalyst*, normal condensation products (292). This emphasizes the fact that the alkylation by metal halides is essentially an activation reaction occurring when suitable activity of the nuclear hydrogen and the aliphatic halogen are realized. This throws new light on the mechanics of the reaction (292) (see the discussion of mechanism, p. 378).

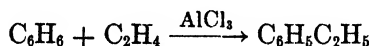


2. *Alkylation by unsaturated substances.* By using one of the active metal halides, it has been found possible to introduce alkyl groups into various nuclei by means of unsaturated compounds. The reaction may be represented by a simple equation using benzene as a type-reactant.



where R and R' are either hydrogen or a radical. Actually, the reaction has been observed not to take place unless hydrogen chloride is present (275). This indicates the prior formation of an alkyl halide followed by the normal course of alkylation as discussed above (437).

As early as 1879 Balsohn (10) showed that olefins reacted with benzene in the presence of aluminum chloride to yield alkylbenzenes.



Because of the availability of ethylene, the reaction was studied more closely later. Fair yields of ethylbenzene may be obtained by passing a stream of ethylene into a rapidly stirred suspension of finely pulverized aluminum chloride in benzene (275). It was found that the higher ethylated benzenes could be prepared by varying the reaction conditions. Prolonged reaction favored a higher yield of polyethylbenzenes, including pentaethylbenzene.

The higher members of the olefin series behave in a similar manner (10, 144, 54). The benzene ring adds to the carbon atom holding the least number of hydrogen atoms.

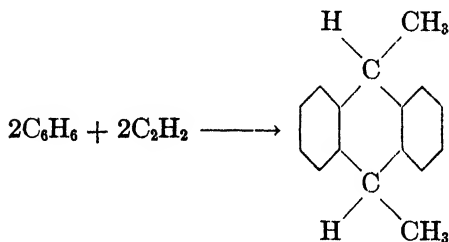
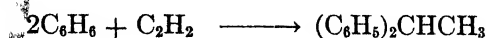
With cyclic olefins alkylation occurs to yield cyclic alkyl groups in the nucleus (26). For example, cyclohexene yields with *p*-cymene, 2-cyclohexenyl-4-isopropyltoluene.

Niederl and coworkers (299)<sup>2</sup> have demonstrated that it is unnecessary to use vigorous reagents like aluminum chloride when phenolic compounds are being substituted. A condensing agent such as sulfuric acid dissolved in acetic acid is satisfactory to realize an efficient alkylation of phenols and cresols.

<sup>2</sup> Leading references may be found here.

Certain negatively substituted benzenes are also alkylated by olefins. Nieuwland and co-workers have demonstrated that boron trifluoride will introduce propyl groups into salicylic acid (72), as well as into activated benzene nuclei like the phenols (405), to yield mono- and di-alkylated substances. The entering alkyl groups are oriented normally, i.e., ortho and para to the hydroxyl group and meta to the carboxyl group.

Not only olefins behave in this manner, but acetylenes yield the predicted compounds by the addition of two aromatic nuclei to give a diaryl or related compound. Acetylene reacts in the presence of aluminum chloride to yield *as*-diphenylethane and 9,10-dimethyl-9,10-dihydroanthracene (62, 34, 12).



Toluene and chlorobenzene yield the corresponding compounds, and dimethylaniline gives a small quantity of *as*-(*p*-tetramethyldiaminodiphenyl)ethane. Nitrobenzene and ethyl benzoate give no products. These latter facts are not disturbing, since highly negative groups markedly retard or prohibit the Friedel-Crafts reaction in general (see the discussion of activating and inhibiting groups, on p. 370).

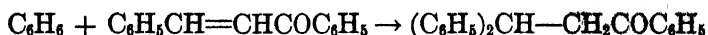
That acetylene reacts with benzene progressively as expected, that is, first to give styrene, then to yield the final products, finds support in the fact that styrene (433a) and polymers of styrene have been found in the reaction (34). Further evidence is found in the isolation of vinylresorcinol from the reaction of acetylene and resorcinol in the presence of a mercury sulfate-sulfuric acid catalyst (113a).

The halogenoolefins behave as might be expected, when it is considered that they contain both aliphatically bound halogen and a double bond. Vinyl chloride yields with benzene and aluminum chloride *as*-diphenylethane and a small quantity of 9,10-dimethyl-9,10-dihydroanthracene; *as*-dichloroethylene yields the normal product, triphenylethane, and two other products, *s*-diphenylethane and *s*-tetraphenylethane (12, 33, 75). The reaction appears to proceed through a monoarylhalogenoethane (33).

With allyl chloride and benzene, ferric chloride or zinc chloride gives

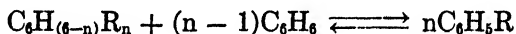
1,2-diphenylpropane and 2-chloro-*n*-propylbenzene. Freshly sublimed aluminum chloride yields as the sole product 1,2-diphenylpropane. This is in contrast to aluminum chloride which contains a little moisture. The latter substance produces, with benzene and allyl chloride, propylbenzene and 9,10-diethylantracene (see the discussion of condensing agents, on p. 374).

The general course of the reaction is not affected by the presence of such radicals as may contain the carbonyl group (437, 459, 94, 441, 128).



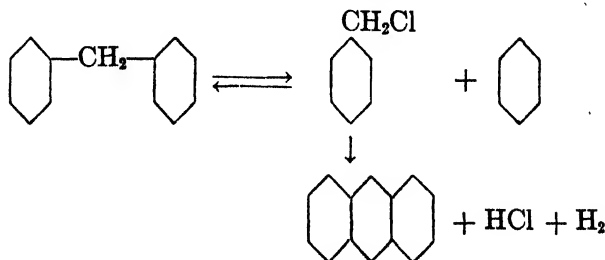
3. *Alkylation by hydrocarbons.* As early as 1885, it was shown that the Friedel-Crafts alkylations were reversible (5). Methyl groups were found to rearrange from one nucleus to another. Polymethylated benzenes were obtained from toluene or *m*- or *p*-xylene. *o*-Xylene did not rearrange with aluminum chloride.

In an extended study, Boedtker and Halse (29) found that the mass law affected the movement of alkyl groups. Large quantities of alkylating agent and condensing agent tended to give polysubstituted benzenes, while the reverse conditions gave monoalkylated substances. This reversibility may be represented as follows, where R is an alkyl group:



As the weight of the alkyl group increases, the ease of rearrangement increases. Thus the polyamylbenzenes alkylate benzene with great ease (29). With *p*-cymene, aluminum chloride transplants the methyl as well as the isopropyl group to yield benzene, toluene, *m*-xylene, *s*-tetramethylethane, and 3,5-diisopropyltoluene (385).

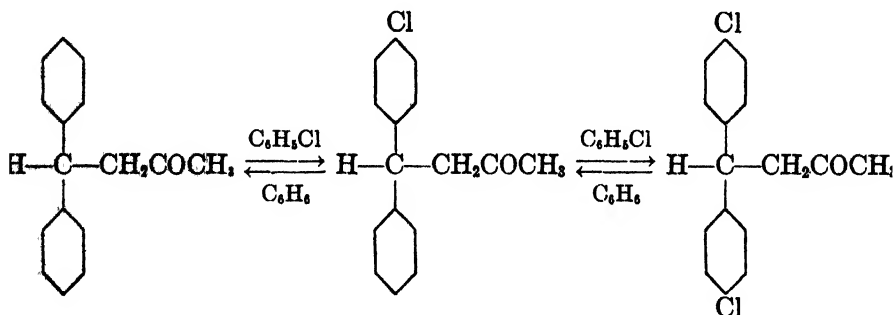
The heavier hydrocarbons tend to give this same type of reaction. Diphenylmethane, for example, gives anthracene when treated with aluminum chloride. This is offered in support of the theory of splitting, followed by recombination of part of the reactants (344).



Naphthalene also may be alkylated by means of hydrocarbons. Diethyl-

benzene, naphthalene, and aluminum chloride give as the principal products ethylnaphthalene and ethylbenzene.

In an extended and detailed study of the reversibility of the Friedel-Crafts alkylations, Fuson and coworkers (459, 94, 441, 128, 188) have shown that the heavy hydrocarbons are applicable to the equilibrium reactions, the aryl nuclei may contain certain so-called negative substituents, and the aryl radicals are apparently replaced mole for mole by the new aryl group. An example is the stepwise interconversion of benzo-hydrilacetone and di-*p*-chlorobenzohydrilacetone.



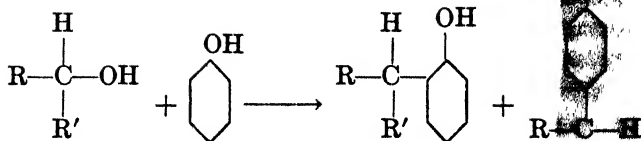
Di-*p*-methylbenzohydrilacetone behaves in a similar manner (459).

Benzene itself may introduce various alkyl groups into aromatic nuclei. On refluxing benzene with aluminum chloride, ethylbenzene (206) and cyclohexylbenzene (443) may be isolated, among other products. This is further discussed under the subject of mechanism (p. 378).

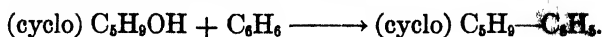
In attempts to alkylate naphthalene using saturated paraffins, no alkylnaphthalenes were isolated (300), indicating an absence of reactivity on the part of the paraffins.

4. *Alkylation by alcohols.* Alcohols will alkylate certain aromatic compounds in the presence of active metal halides. It is not clear whether an alkyl halide is formed as an intermediate or whether the reaction is essentially a dehydration, since it is well known that sulfuric acid will bring about a similar alkylation.

Zinc chloride (109, 149) or aluminum chloride seem to give identical reactions (202, 203). However, aluminum chloride alkylates by means of an alcohol only where there is a "strained" carbon atom attached to the hydroxyl (203). Phenyl groups, high degrees of branching, or strained rings so activate alcohols that they readily undergo a reaction with an aromatic nucleus. Thus saturated primary alcohols or cyclohexylcarbinol do not react, while phenyl- or cyclopentyl-carbinols do alkylate benzene in the presence of aluminum chloride.



where R is aryl and R' is hydrogen or alkyl.

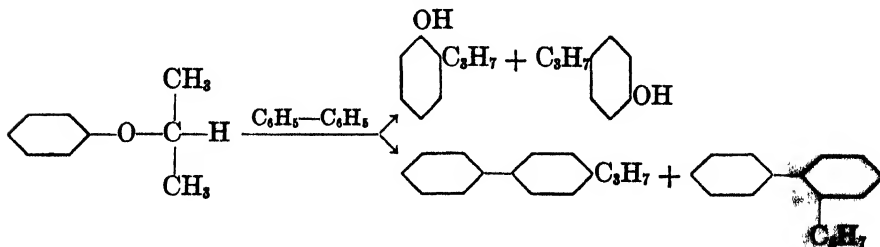


5. *Alkylation by ethers and esters.* It is well established that aromatic ethers will rearrange to yield alkylated phenols under a variety of conditions (401, 299, 72, 405). In some instances heat alone is sufficient to bring about the rearrangement (401, 288). In view of this ease of cleavage of the oxygen linkage in ethers, it is not surprising to find that aliphatic or mixed ethers will alkylate certain types of compounds by means of the Friedel-Crafts reaction. Aliphatic ethers give well-defined products with aromatic nuclei (214, 407).



where R is an alkyl group.

In showing that the rearrangement of mixed ethers, such as isopropyl phenyl ether, is not necessarily bimolecular (288), it was demonstrated that with acidic reagents such as zinc or aluminum chlorides the reaction becomes complex and that the alkyl group of the ether apparently splits off to yield an alkyl halide which will alkylate the newly formed phenol or a foreign molecule (288, 402). Isopropyl phenyl ether yields, with aluminum chloride and diphenyl, *o*- and *p*-isopropylphenol, phenol, and *o*- and *p*-isopropylidiphenyl.



Fifty per cent of the products is represented by the substituted phenols. *s*-Dibromodimethyl ether behaves as methylene bromide (343). In the reaction with benzene the final products are identical with those that would result with benzene, aluminum chloride, and methylene bromide.

Since esters contain a modified ether linkage, it is not surprising that they, too, alkylate in the Friedel-Crafts reaction. It was observed in 1877 that ethyl chlorocarbonate would introduce an ethyl group instead of an acyl group (112). This early observation has been followed by the use of esters as alkylating agents. A variety of esters will introduce alkyl groups. Alkyl esters of aliphatic acids (235, 214), boric acid (216), chlorocarbonic acid, and sulfonic acids (58) all introduce alkyl groups in a manner similar to alkylation by alkyl halide.

This type of alkylation offers great possibilities for the alkylation of highly sensitive types, since the complex formed between the ether or ester and the condensing agent materially lessens the drastic resinifying and polymerizing action of the anhydrous condensing agents such as aluminum, stannic, or zinc chlorides. In fact, it has been possible to realize syntheses in the thiophene series by means of ethers where all efforts with alkyl halides have failed (407).

In connection with alkylation by esters, it is interesting to note that ethyl nitrate introduces the nitro group instead of the alkyl group (28). The behavior of this ester, for some reason, appears to illustrate a case of an anomalous reaction. Indeed, it is possible that the ethylbenzene did form but in exceedingly small quantity, since nitration may be a more rapid reaction under the experimental conditions.

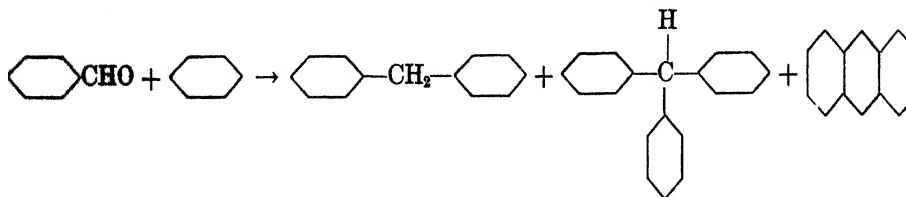
6. *Alkylation by oxides, aldehydes, and ketones.* As another group of unusual alkylating agents, we find that alkyl oxides, aldehydes, and ketones will introduce the corresponding substituted or unsubstituted alkyl groups.

Ethylene oxide yields with benzene and aluminum chloride a small quantity of  $\beta$ -phenylethyl alcohol and a large quantity of *s*-diphenylethane (365).



Homologs of ethylene oxide behave in a similar manner (432).

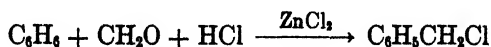
Both alkyl- and aryl-aldehydes will alkylate benzene. Generally the product is an alkylated hydrocarbon containing two or three aryl groups. For example, benzaldehyde yields diphenylmethane, triphenylmethane, and anthracene, which is a product from the benzaldehyde alone (365).





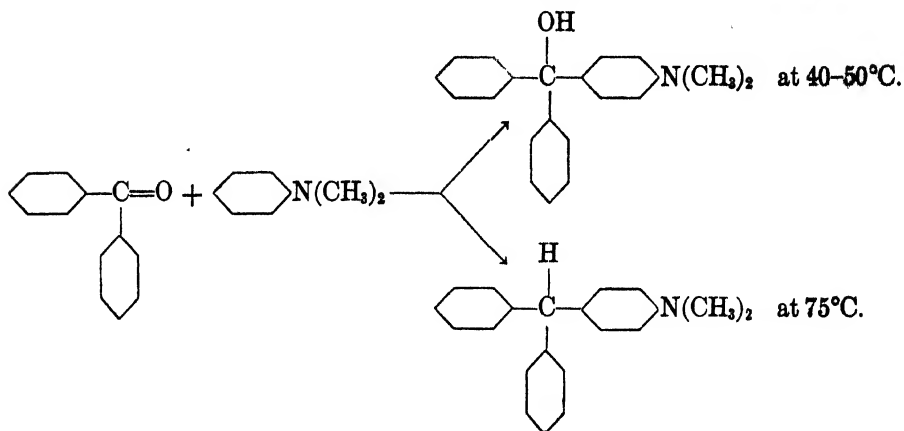
In a similar manner, the straight chain aliphatic aldehydes yield alkylated hydrocarbons with *unbranched* chains. Aldehydes with one (115, 197, 287), two, three, four (22), and five (365) carbon atoms have yielded this type of reaction.

If formaldehyde is used with hydrogen chloride and zinc chloride in benzene solution, benzyl chloride results (362).



Chloral, bromal, and their hydrates behave in the predicted manner to yield condensation products with the formyl group, the halogens, or both (115, 116, 117).

Since it is undoubtedly the activity of the carbonyl group that accounts for alkylation by aldehydes, it is naturally anticipated that ketones would behave in a similar manner. This is the case, for ketones yield carbinols at lower temperatures and hydrocarbons at higher temperatures (67, 436).



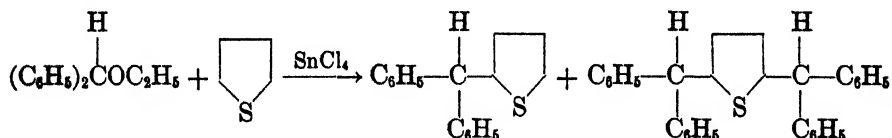
7. *Relative reactivities of the various alkylating agents.* Unfortunately no rigorous experimental comparison of the activity of the various alkylating agents has been made. However, conclusions from the meagre information available tend to show that alkyl attached to halogen is perhaps the most reactive alkylating group. The danger in attempting to correlate relative activities from a survey of the literature lies in the fact that the catalyst may vary in regard to purity. The solvent may vary in the same way, and conditions of reaction, such as stirring, particle size, solubility of reactants, temperature, and oxygen exclusion, may vary to a marked degree. All of these factors affect the reaction.

The conclusion is not to be drawn that all aromatic nuclei undergo alkylation. So far nitrobenzene, unsubstituted benzoates, and simple

phenyl nuclei in ketones and nitriles have not been alkylated. The presence of so-called negative groups appears to inhibit reaction, if indeed they do not completely prohibit substitution in the Friedel-Crafts reactions. (See the discussion of activating groups, p. 370.)

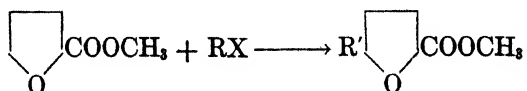
### B. Alkylation of the heterocyclic rings

Very little work has been published on the alkylation of heterocyclic compounds. This is explainable, partly, by the sensitivity of the substances. Generally, the heterocyclic compounds contain oxygen, sulfur, or nitrogen linkages. For this reason these compounds are either highly sensitive to drastic condensing agents, or they form complexes with the metal halide so that substitution in the Friedel-Crafts reaction is inhibited. Attempts to acylate unsubstituted heterocyclic rings, such as pyrrole, thiophene, or furan, have been fairly successful. On the other hand, attempts to *alkylate* these unsubstituted rings have been generally unsuccessful. The apparent exception is the case of thiophene, which, when treated with stannic chloride and benzohydril ethyl ether, yields 2-benzohydrilthiophene and 2,5-dibenzohydrilthiophene (407) (compare also references 416 and 417).



When benzohydril chloride was substituted for the ether, no alkylated product was obtained.

It has been found (144) that no direct alkylation of furan itself occurs. An easy approach to the 2-alkylfurans through the Friedel-Crafts reaction was found in the discovery that methyl 2-furoate would alkylate smoothly to yield methyl 5-alkyl-2-furoates. This product could be hydrolyzed to the acid, which could in turn be decarboxylated to yield the 2-alkylfuran (144).

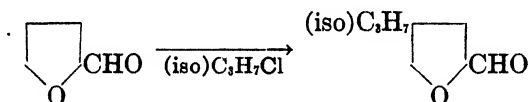


where R and R' are isomeric alkyl groups. An interesting fact in this connection was established by the observation that methyl and ethyl halides would not alkylate the esters of furoic acid. Perceptible alkylation began with the propyl halides and extended at least through the hexyl halides. The yields in these reactions were excellent (144), and it is now possible to obtain almost quantitative yields with propyl and butyl halides (53).

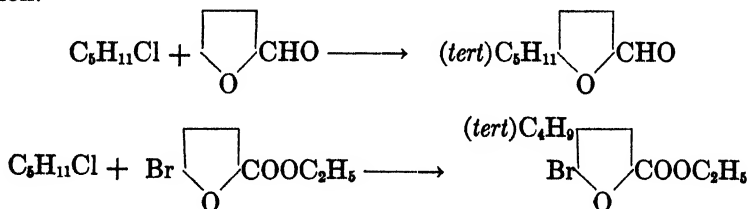
In every case, the product isolated contained the most highly branched alkyl groups possible. For example, normal-, iso-, secondary-, and tertiary-butyl halides give the same product in this reaction,—5-*tert*-butyl-2-furoic acid esters. This rearrangement of the alkyl group is in line with observations on the alkylation of benzene.

Ketones of furan were observed to undergo alkylation in a similar manner. When phenyl 2-furyl ketone was used, the alkyl group entered the furan ring. These alkylations, coupled with the fact that corresponding benzene compounds, methyl benzoate for example, do not undergo alkylation under corresponding conditions, and that benzene may be used as a solvent for Friedel-Crafts reactions in the furan series (346 to 378) have been discussed at length elsewhere (144).

Furfural also was found to undergo the Friedel-Crafts alkylation (146). This was surprising when it is considered that furfural is highly sensitive to acid substances (143a, 54). The alkylation took a course that was unprecedented in furan chemistry. Hitherto in every case when a mono-substituted furan was further substituted, the entering group went to either the 2- or the 5-position (143a). In this alkylation, using isopropyl chloride, the group enters the 4-position (146, 147).

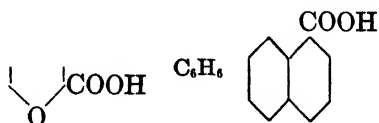


As indicative as the above studies were of the unreliability of Friedel-Crafts alkylations, the interesting observation has been made that when the higher homologous halides, like the variously branched butyl or amyl chlorides, are used to alkylate furfural, the group enters not the 4- but only the 5-*position*. Furthermore with certain furanic compounds, in addition to the isopropyl residue (146, 147) no group except the tertiary-butyl group has been introduced (145c), regardless of whether the starting reagents were butyl, amyl, or hexyl halides. This indicates that with amyl and hexyl halides methylene groups are eliminated somewhere in the reaction.



With benzene and aluminum chloride, 2-furoic acid (146) and methyl 2-furoate (146a) yield  $\alpha$ -naphthoic acid and methyl  $\alpha$ -naphthoate, respec-

tively. The latter reaction produced also a quantity of an indefinite high molecular weight ester of undetermined constitution (144a, 218).

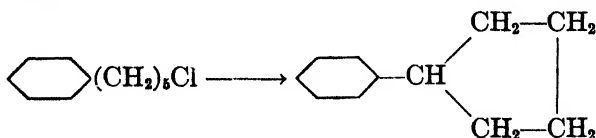


### C. The alkylation of aliphatic compounds

When considered from the standpoint of smoothness of reaction, yield, ease of control, and general practicability, the Friedel-Crafts syntheses are essentially transformations that apply to the so-called aromatic nuclei. But as has been pointed out (144), the divisions generally made in substitution reactions such as aliphatic, aromatic, and heterocyclic, are divisions based essentially on rates rather than on the kind of reactions, and those that are commonly considered as typically aromatic find their counterparts in the chemistry of aliphatic substances. So it is with alkylation by the Friedel-Crafts syntheses.

Relatively few cases have been reported of the alkylation of aliphatic types. Yet the significant fact remains that well-authenticated examples have been reported in which aliphatically bound hydrogen is replaced by alkyl groups under the influence of such condensing agents as aluminum chloride. As has been mentioned above, the very first report of the Friedel-Crafts reaction concerned the replacement of hydrogen in an aliphatic substance. This observation was made by Friedel and Crafts in 1877 (119).

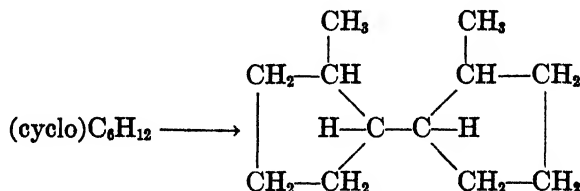
One of the first clean-cut aliphatic alkylations was reported in 1912 by von Braun (49). It was observed that attempts to bring about ortho intra-ring closures of 5-phenyl-*n*-amyl chloride did not yield the expected substance, but gave instead cyclopentylbenzene in 85 per cent yields.



In later communications (47, 48), it was shown that reaction undoubtedly did not take place by eliminating hydrogen chloride from the adjacent terminal carbon atoms followed by an isomerization of the 5-phenylamylene-1. All attempts to isomerize 5-phenylamylene-1 to cyclopentylbenzene led to polymeric substances.

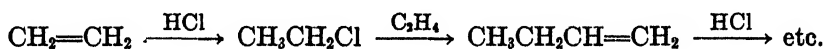
An attempt to alkylate cyclohexane by using ethyl, *n*-propyl, isopropyl, isobutyl, and cyclohexyl halides as well as chloroform and carbon tetra-

chloride with aluminum chloride as the condensing agent, led to indefinite, saturated and unsaturated hydrocarbons (296). Interestingly enough, however, cyclohexane was isomerized and coupled to yield 2-methylcyclopentyl-2-methylcyclopentane.



This interesting case of rearrangement is a commonly observed one, which is discussed at greater length elsewhere in this paper.

In attempting to establish the mechanism of polymerization of simple, low molecular weight olefins by aluminum chloride to yield lubricating oils, it has been suggested that actually a series of alkylations occurs, which results in the formation of long-chain saturated or near-saturated compounds (409, 285, 286).



The process represented by the above reaction is only an early step in a series of reactions which involves addition of hydrogen chloride to butylene-1, followed by reaction with another molecule of ethylene and so on until high molecular weight oils are formed.

### III. ACYLATION

#### A. Aromatic types

1. *The introduction of the keto group by various reagents.* By far the greatest amount of work on the Friedel-Crafts syntheses has been done on the reactions that introduce acyl groups. This is particularly true of the introduction of the keto group. This extensive study has produced a literature that is especially rich in details which give a rather complete picture of the reaction.

The stimulus to close study of acylations has resulted from several factors. One of the foremost actuating influences has been the demand for ketones of varied nature for industry, particularly as dye intermediates. Furthermore, the acylations lend themselves to a relatively simple and facile study, since they are easy to control and give, generally, monoacylated products. These facts render the reactions highly practical and obviously of value for routine laboratory or industrial syntheses, since

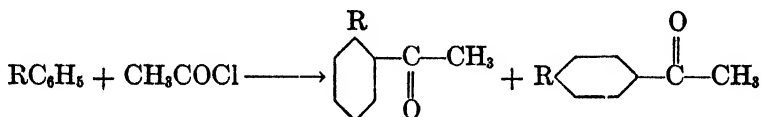
many of the acylations give yields of 80 to 97 per cent of the theoretical quantity of products.

(a) Acyl halides. The general reaction for the introduction of keto groups may be simply formulated using benzene, aluminum chloride, and an acyl halide.



where R' is alkyl or aryl and R is aryl.

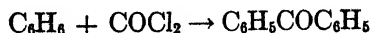
It was early realized (119, 121, 122) that alkylations had their counterparts in acylation by means of the Friedel-Crafts syntheses. It was observed that acetyl chloride would undergo a condensation with benzene, or alkylbenzenes, and aluminum chloride to give ketones in good yield (122, 270, 293, 257, 136).



where R = hydrogen or alkyl. The higher acyl halides behave in a similar manner (291a, 144, 136, 220). Propionyl, butyryl, and caproyl halides yield ketones with alkyl groups of configurations which correspond to the branching of the alkyl group in the acid halide. For example normal- or iso-butyryl chlorides will yield with benzene and aluminum chloride the corresponding normal- and iso-propyl phenyl ketones, respectively. This absence of side chain rearrangement has made acylations by active metal halides doubly valuable, since on subsequent reduction the ketones give good yields of hydrocarbons of predicted configuration. Johnson's work (211a) on the synthesis of the alkylresorcinols has emphasized this point. Thus direct access is had to the normal or variously branched homologs of benzene and its derivatives.

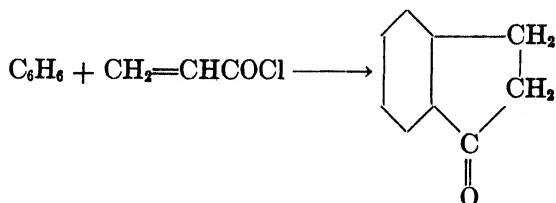
Not only do the branched acyl halides undergo this condensation, but the cyclic acid halides behave in a similar manner. With benzene and aluminum chloride, cyclopropanecarboxylic acid chloride gives an excellent yield of phenyl cyclopropyl ketone (220).

Besides the fatty acid halides, other types may be utilized. It was early shown that carbonyl chloride would give the expected ketones (2, 121, 453).

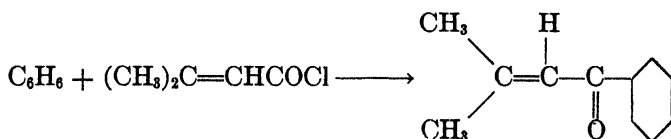


This ketone synthesis seems to be generally applicable to unsaturated acid halides, although some halides unavoidably give complicating reactions on

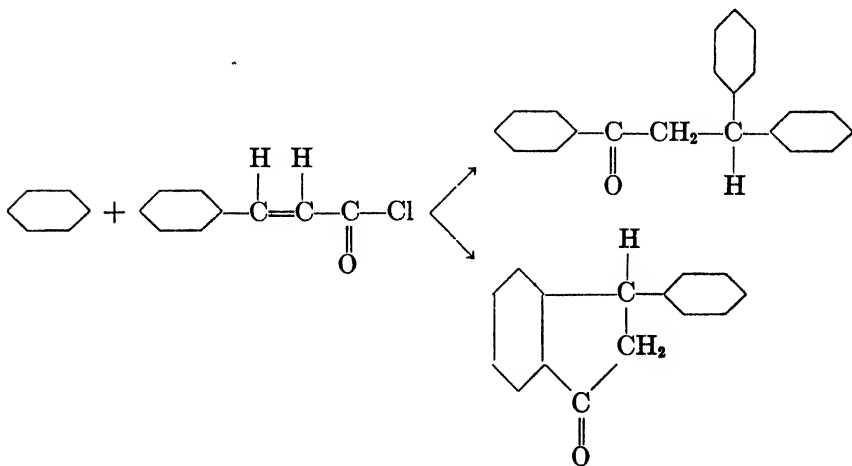
account of the unsaturation. For example, acryloyl chloride yields hydrindone and not vinyl phenyl ketone (225a).



The higher unsaturated acid halides yield the expected unsaturated ketone. 2,2-Dimethylacryloyl chloride gives a 40 per cent yield of 2,2-dimethyl-vinyl phenyl ketone (77).



Cinnamoyl chloride behaves as might be predicted on the basis of the presence of an ethylenic linkage and an acyl halide grouping. With benzene the tendency is to yield 2,2-diphenylethyl phenyl ketone and 3-phenylhydrindone-1 (225).

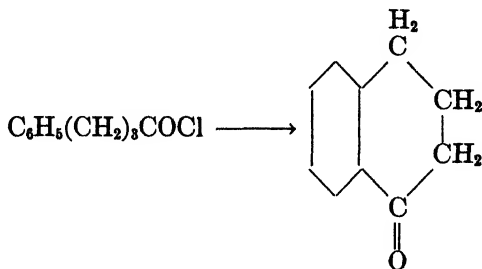


However, bromobenzene, diphenyl ether (225), diphenyl (7), or methoxy compounds (397, 398) give principally the expected para-substituted unsaturated ketones.

Phenylpropionic acid chloride yields an acetylenic ketone (397). The

halogeno fatty acid halides react to yield the corresponding halogenoalkyl aryl ketones. For example, 1,2-dibromopropionyl chloride and benzene give 1,2-dibromoethyl phenyl ketone (225a).

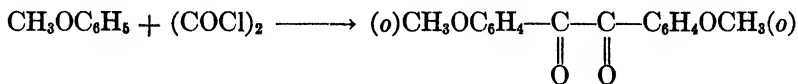
When phenyl nuclei are substituted into the alkyl groups of the longer fatty acids, their halides may undergo a ring closure (259).



When oxalyl chloride is used in the synthesis of ketones, the nature of the product depends in a large measure on the substance undergoing substitution. Compounds that acylate with relative ease yield diketones, while substances that acylate with difficulty yield simple ketones as a result of the rapid decomposition of the oxalyl chloride by the condensing agent. This decomposition follows a course that yields carbon monoxide and carbonyl chloride. The latter decomposition product reacts normally to yield a monoketone (414).



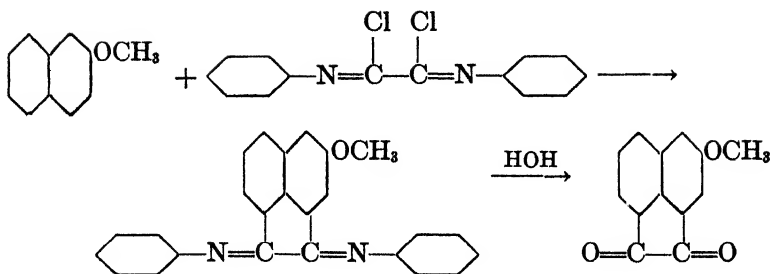
With a more active nucleus, such as anisole or dimethylaniline, a diketone results, since the substitution proceeds more rapidly than the decomposition of oxalyl chloride (410, 411, 244).



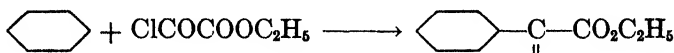
In this connection, it is interesting to note that oxalyl bromide will give a very small yield of benzil when condensed with benzene and aluminum halide, although the oxalyl chloride does not (410).

The synthesis of diketones may be effected in poor yields by using diphenylimidochlorides of oxalic acid. Here again, only the more active nuclei such as anisole or the alkoxynaphthalenes, allow substitution (412). Methoxynaphthalene, upon reaction with the diphenylimidochloride of oxalic acid and aluminum chloride, gave, after hydrolysis, methoxy-acenaphthenequinone.



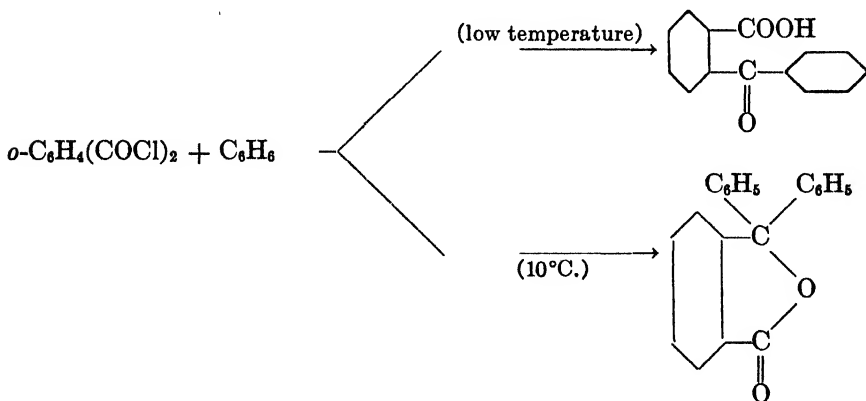


An approach to the substituted keto acids may be realized by using the half-ester of oxalyl chloride. For example, ethyl chloroglyoxylate with benzene and an active metal halide will yield ethyl phenylglyoxalate (335).



The aromatic acyl halides behave in the expected manner to yield diaryl ketones. Benzoyl chloride will give excellent yields of ketones with the substituted or unsubstituted nuclei (132, 177). Substituted benzoyl halides behave in a similar manner (278, 391).

Phthalyl chloride reacts in its two isomeric forms (63). At very low temperatures, the product with benzene and aluminum chloride is *o*-benzoylbenzoic acid. At 10°C. or above the product is diphenylphthalide.

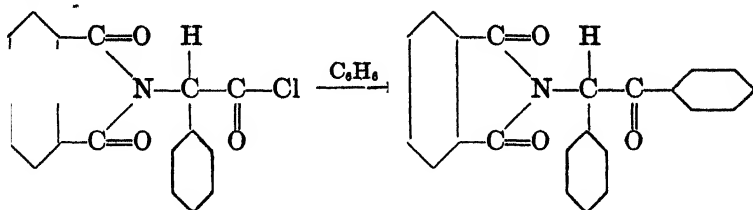


With a large excess of benzene at higher temperatures, the products are *o*-triphenylmethylbenzoic acid and 9-diphenylanthrone (63).

With *o*-carboethoxybenzoyl chloride, the product from benzene and aluminum halide is the expected ethyl *o*-benzoylbenzoate (403).

Aminoketones may be synthesized by this reaction if the amino group

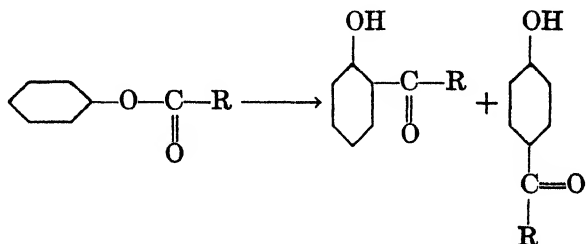
is protected by acylation. A modified Gabriel phthalimide synthesis of amines may be used as follows (106).



In general, the aromatic substances which will undergo acylation to introduce a keto group are those that undergo alkylation. The typical classes are, besides the unsubstituted nuclei, the halogenobenzenes (132), aromatic ethers (136), biphenyl (59, 393), amines (274a, 410), alkylbenzenes (2, 270), and hydroxybenzenes (20, 126, 458, 143).

Usually the so-called negative groups that contain double bonded oxygen inhibit acylations of the benzene nucleus. This inhibiting action may be overcome in part by the presence of activating groups, such as hydroxyl, alkoxy, or methyl. Thus benzaldehyde, benzoic acid and its esters, unsubstituted phenyl ketones, and nitrobenzene do not, generally, undergo acylations. This behavior is discussed at greater length in the section on activating groups.

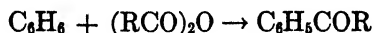
In any discussion of the introduction of keto groups by metal halides, the Fries reaction must be considered. Although it is customary to consider the Fries reaction as separate and distinct from the Friedel-Crafts syntheses, it is difficult to differentiate accurately, since the Friedel-Crafts synthesis of ketones from phenols may, and in many cases does, pass through the intermediate formation of phenyl esters (356). The Fries transformation is essentially the rearrangement of esters of phenols and related compounds to hydroxyketones. This reaction is generally carried out in an inert solvent like carbon disulfide or nitrobenzene, and is actuated by active metal halides, such as aluminum or ferric chloride.



Fries and Finck reported in 1908 that aluminum chloride would rearrange the esters of phenol to yield aryl alkyl or diaryl ketones (126). The esters

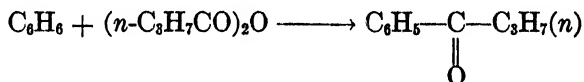
of polyphenols like resorcinol undergo rearrangement to yield polyketo substances (9). The substituted phenyl esters behave in a similar manner, to yield the corresponding substituted ketone (355).

(b) Anhydrides. Generally anhydrides react with an aromatic nucleus to yield one equivalent of ketone for each mole of anhydride when two equivalents of aluminum halide are used (302, 181, 359).



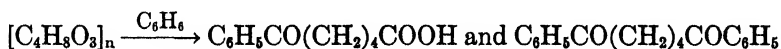
This is a rough picture, although the fate of the remaining fragments of the anhydride is important, since it has recently been demonstrated that these fragments may in part also acylate the ring to increase the yield (159). This angle of the problem is further discussed under the subject of the mechanism of the reaction (p. 378).

The simple aliphatic anhydrides behave as expected, to yield the alkyl aryl ketones (302). Using *n*-butyric anhydride the reaction may be represented by the following equation.



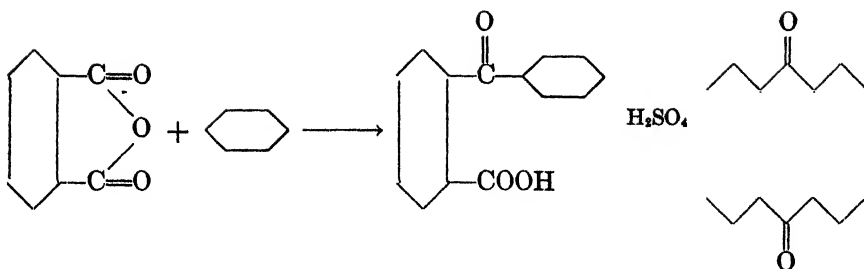
The absence of rearrangement in the alkyl group is to be noted.

When polyanhydrides are used, for example, those of adipic or sebacic acids, the products with benzene and aluminum chloride are  $\omega$ -benzoyl acids and  $\alpha$ ,  $\omega'$ -dibenzoylated hydrocarbons (181).



Benzoic anhydride may be used in a similar manner to yield diaryl ketones (70, 359). Of the aromatic anhydrides, the most valuable is phthalic anhydride. In fact there are few reactions of organic chemistry that have meant more to industry than the formation of *o*-aroylbenzoic acids from phthalic anhydride and an aromatic nucleus in the presence of an active metallic halide, generally aluminum chloride. By means of sulfuric acid, the *o*-aroylbenzoic acids may undergo ring closure to yield various quinones which are prepared in large quantities as dye intermediates.

Although early observations showed the feasibility of using aluminum chloride and phthalic anhydride for the synthesis of anthraquinone and naphthanthraquinone (1), it is only comparatively recently that large quantities of these dye intermediates have been prepared by this reaction (6). This synthesis may be represented by a simple equation:



As a result of the absence of impurities, the commercial anthraquinone prepared by this reaction is superior as a dye intermediate to the anthraquinone obtained by the oxidation of anthracene (329) by chromic acid; it is also less expensive than that derived from crude anthracene by catalytic oxidation.

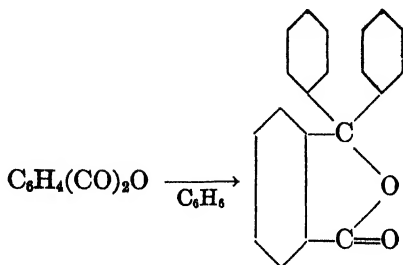
The phthalic anhydride approach to anthraquinone or its simple derivatives is essentially a quantitative transformation from phthalic anhydride and benzene to *o*-benzoylbenzoic acid. It has been demonstrated that actually 97 per cent of the theoretical quantity of *o*-benzoylbenzoic acid may be isolated (176, 359, 2, 54).

A variety of nuclei will condense with phthalic anhydride to give the corresponding *o*-aroylbenzoic acids. Benzene (159, 254), toluene (239, 176), halogenobenzenes (156, 284), halogenotoluenes (176, 175), diphenyl (161, 86, 378), aromatic ethers (350), naphthalene (176), substituted naphthalenes (178), anthracene (1, 129, 151, 176, 178), phenanthrene (178), and fluorene (74) all undergo acylation by phthalic anhydride and aluminum chloride. Here again we find that highly negatively substituted nuclei, such as benzaldehyde, benzoic acid and its esters, phenyl ketones, and nitrobenzene, do not undergo acylation.

The phthalic anhydride may contain a variety of substituents, the nature of which does not affect the course of the reaction. In every case, regardless of the substituents present in the phthalic anhydride, the product is a substituted *o*-benzoylbenzoic acid. Some of the substituted phthalic anhydrides that have been used contained the following substituents: 4-bromo- (420), 4-nitro- (240), 4-acetamino- (240), tetrachloro-, tetrabromo-, tetraiodo- (239), 3-sulfo-, and 4-sulfo- (390).

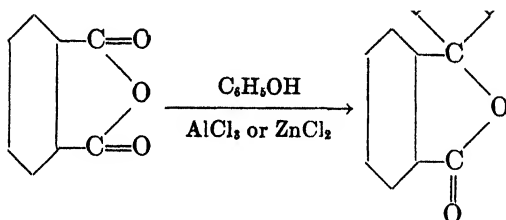
The phthalic anhydrides may condense in another manner, since simultaneously with *o*-aroylbenzoic acid formation, there may be phthalide formation (331). It has been noticed that under adverse conditions of reaction, the yield of *o*-benzoylbenzoic acid is reduced and phthalides tend to form instead (359). Some foreign substances, such as acetic anhydride (241), or non-equivalent quantities of the reactants (359) favor the formation of phthalides. In fact the addition of acetic anhydride may increase

the yield of phthalides to 93 per cent of the theoretical, with no keto acid formation (241).



On the basis of the phthalide formation, it is not surprising to find that phenolphthalein may be synthesized by the reaction of excess phenol and phthalic anhydride in the presence of aluminum halide (439). Zinc chloride with better results and ferric chloride with poorer results may be substituted for the aluminum chloride.

OH   OH



(c) Ketenes. The highly unsaturated ketene reacts with an aromatic nucleus in the presence of aluminum halide to yield ketones. This is not unusual, since ketene in acylation may be compared with ethylene in alkylation. Both add hydrogen halide and both yield reaction products in the Friedel-Crafts reactions as if prior addition of hydrogen halide occurred.

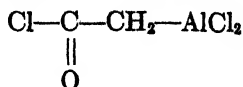


The general case for the reaction of ketene with benzene and aluminum halide may be represented by a simple transformation.



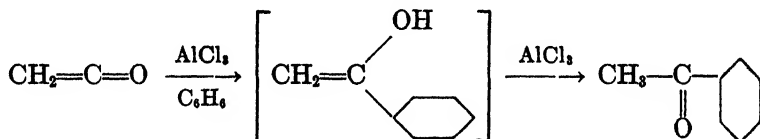
It is not clear whether there occurs direct addition to the ethylenic linkage, the prior formation of acetyl chloride, or the intermediate formation of an

organoaluminum compound (319). That is,



may be formed. Although there is little direct experimental evidence, a consideration of the known facts seems to indicate the intermediate formation of acetyl chloride. First, the general information on ketene fails to indicate that direct addition to the ethylenic linkage occurs. Secondly, the direct addition of nuclei to an ethylenic linkage in the Friedel-Crafts reactions has not been verified. Thirdly, no case of the definite intermediate formation of an organoaluminum compound has been demonstrated in the Friedel-Crafts reactions. Fourth, the presence of hydrogen halide appears to increase the yield of ketone when ketene is used as the acylating agent (333).

There is, of course, the possibility that a preliminary addition to the carbonyl group is followed by rearrangement. However, there is no evi-



dence to support this view in regard to the Friedel-Crafts reaction.

Benzene, anisole, naphthalene (201), or veratrole (333) may be acylated by ketene, while the negatively substituted benzenes like acetophenone again fail to undergo acylation (201).

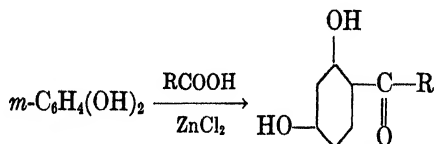
(d) Acids and esters. Access to the ketones may be had through carboxylic acids. It is possible to introduce the keto group by condensing aliphatic and aromatic acids with nuclei in the presence of active metal halides.

The aliphatic acids, such as acetic or propionic, when heated with excess of aluminum chloride in benzene give ketones in good yields, 60 to 80 per cent (157). The evidence strongly indicates that the reaction is not a direct acylation by the acid, but instead there is intermediate formation of acid halide followed by the orthodox Friedel-Crafts acylation. Thus three moles of aluminum halide are required for each mole of ketone formed.

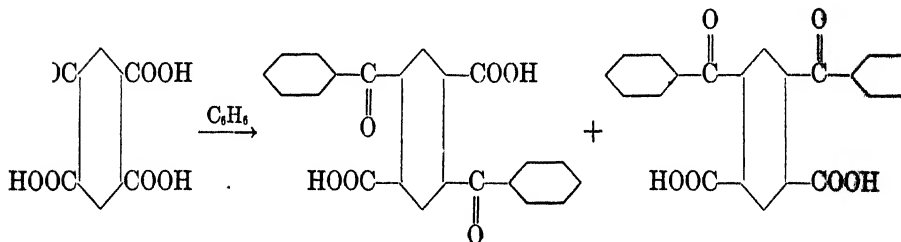


Although this method of ketone synthesis appears to require three times the quantity of aluminum chloride used in acylations by acid halides, the

reaction should prove valuable for commercial work and for industrial syntheses when the inexpensiveness of aluminum chloride is considered (251, 252, 6, 157). Already acids have been applied commercially to the preparation of ketones. A case in point is the preparation of *n*-hexyl-resorcinol, which is acylated and then reduced to the alkylated compound (291b). Zinc chloride gives particularly good results when it is the condensing agent.

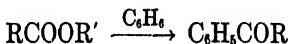


Aromatic acids also acylate under these conditions. Even polycarboxylic acids, such as pyromellitic acid, condense to yield keto acids (328).

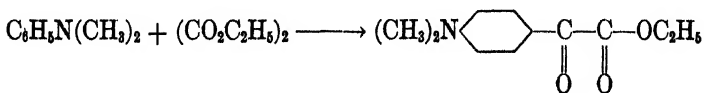


Instead of metallic halides, surface catalysts may be used to bring about a condensation of aromatic hydrocarbons, aromatic amines, phenols, or naphthols with carboxylic acids or their anhydrides to yield ketones. This interesting condensation may be catalyzed by activated carbon, silica gel, and bleaching earths (369) instead of aluminum halide.

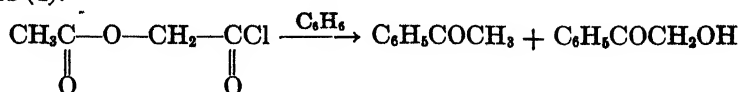
Esters also will acylate aromatic compounds. This reaction has not been extensively studied, but it appears to be of fairly general application. It may occur simultaneously with alkylation by esters.



Such substances as phenyl acetate, *O*-acetylsalicylic acid, or ethyl acetate will yield, with benzene and aluminum chloride, acetophenone (70). *O*-acetylsalicylic acid gives a 70 per cent yield. The dialkylanilines are acylated by diethyl oxalate to give ethyl *p*-dialkylaminophenylglyoxylate in 60 per cent yields (170, 171).

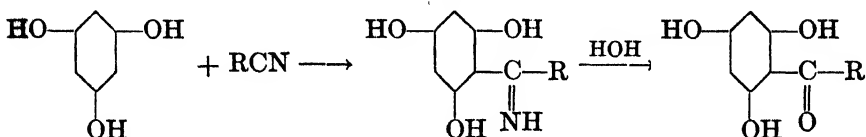


When acetylglycolyl chloride reacts with benzene, an interesting reaction occurs (4).



(e) Nitriles (the Hoesch-Houben reaction). If a nitrile is used as the acylating agent there is formed as an intermediate product a ketimine, which upon hydrolysis yields a ketone; this is termed the Hoesch-Houben reaction. As a distinct reaction from the Friedel-Crafts type it deserves a fuller discussion than can be given here.

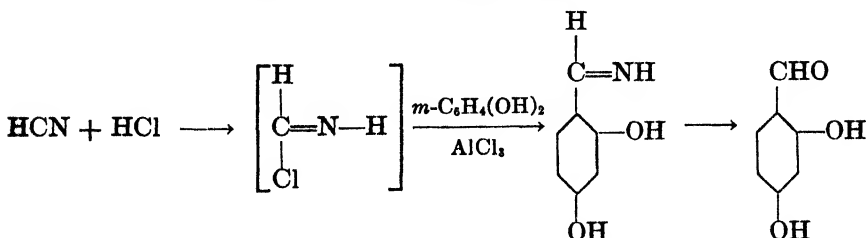
Generally the nitrile is condensed with an aromatic nucleus in the presence of a metal halide such as anhydrous zinc chloride (186).



Aluminum chloride may be used as the condensing agent (234) as well as other active anhydrous metal halides.

2. *Introduction of formyl groups by various reactants.* Actually a formyl group may be regarded as a keto group in which one of the radicals is hydrogen. Therefore, just as acids or acid derivatives condense with various substances by certain anhydrous metal halides to yield ketones, the formyl group is introduced by an acid or its derivatives. In the latter case the acid must contain one carbon atom and be of the fatty acid series. The one substance that fulfills these requirements is formic acid. Thus we find that in every case the formyl group is introduced by formic acid or a derivative of it.

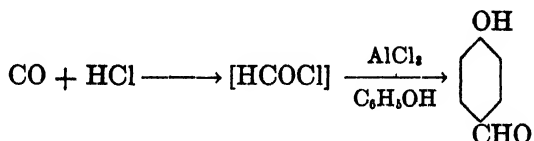
(a) Hydrogen cyanide and hydrogen chloride (the Gattermann reaction). One of the best known reactions for introducing the aldehyde group is by means of the hypothetical formimine chloride formed from the simultaneous introduction of dry hydrogen chloride and anhydrous hydrogen cyanide. In the presence of aluminum chloride, reaction proceeds smoothly to give good yields of the intermediate aldimine, which on hydrolysis yields the aldehyde. The phenols react with great ease (134, 138).





The reaction proceeds at low temperature with the phenols and aromatic ethers (133). More difficulty is experienced in substitutions with the alkylbenzenes or benzene itself. However, it may be accomplished by using higher temperatures and pressures (182).

(b) Carbon monoxide and hydrogen chloride (the Gattermann-Koch reaction). If carbon monoxide is substituted for the hydrogen cyanide in the above reactions, a formyl group may be introduced directly. Formyl chloride is probably formed as an intermediate (139).



An interesting fact established in connection with this reaction is the extreme catalytic effect of a small quantity of cuprous halide when used in conjunction with aluminum chloride.

Nickel carbonyl, possibly as a carbon monoxide carrier, in the presence of aluminum bromide introduces the formyl group into benzene (190).

In quite recent work (157) it has been shown that formic acid will introduce the formyl group directly. This reaction appears to proceed through the formation of formyl chloride by the aluminum chloride. This interesting reaction deserves further study, which it is receiving (161a).



3. *The introduction of carboxyl groups by various reagents.* In general the methods of introducing carboxyl groups depend on a derivative of carbonic acid.

(a) Urea chloride. It is not surprising to find that urea chloride will acylate some aromatic types to yield amides of carboxylic acids. These amides hydrolyze easily, yielding the corresponding acid (137, 140). By this means naphthalene, phenol ethers, and alkylbenzenes have been carboxylated with greater ease than has benzene (140).



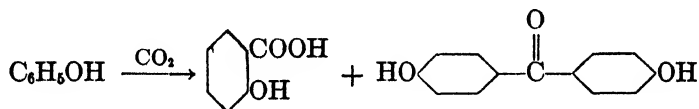
(b) Carbonyl chloride. When carbonyl chloride reacts with the various aromatic types, one of the products is an acid chloride which yields an acid on hydrolysis (2, 121, 453, 274). Any of the various aromatic nuclei that undergo acylations may thus be carboxylated. The yield of acid

depends on the conditions which are adverse to ketone formation, such as low temperature. Small concentration of hydrocarbon or short reaction periods tend to favor acid production.



Since, as has been shown above, oxalyl chloride decomposes under the influence of aluminum chloride to yield phosgene, it is to be expected that acids may form a part of the products in acylation by oxalyl chloride. This is often true. In fact, with diphenyl, *s*-diphenylmethane, retene, or xanthene the product may consist largely of the corresponding acid (245) instead of a ketone or diketone.

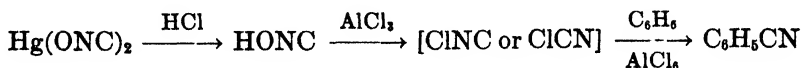
(c) Carbon dioxide. It is interesting that carbon dioxide itself will introduce the carboxyl group in a Friedel-Crafts acylation. The more active nuclei, under high pressures, are required to show any appreciable acylation. Thus the hydroxy- and amino-benzenes react at 70 to 120 atmospheres at 100-150°C. to yield ketones and acids. The catalysts may be anhydrous aluminum, zinc, or ferric chlorides (280).



This reaction has great possibilities. If it were possible to attain acid and ketone syntheses in good yields under conditions easily and cheaply available, the above reaction should prove of inestimable value as an inexpensive avenue to certain acids and ketones.

4. *The introduction of specialized groups.* The definitions of alkyl and acyl groups that have been made for purposes of discussion in this paper place such groups as sulfonyl, hydroxy, thio, thioketo, and others in the class of acyl groups. As has been pointed out earlier, this need not be considered as a hard and fast classification.

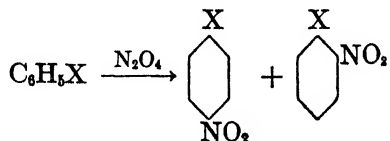
(a) The introduction of the nitrile group. The nitrile group may be introduced into benzene in a direct substitution using aluminum halide. The acylating reactant may be mercury fulminate. This substance may produce fulminyl chloride (or chlorocyanogen) *in situ*, which then reacts to yield benzonitrile (376).



In a similar manner toluene yields *o*- and *p*-toluonitriles.

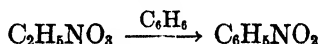
By an analogous reaction, bromocyanogen will yield benzonitrile (123).

(b) Introduction of the nitro group. Nitration may be effected by an aluminum chloride catalyzed reaction. If nitrogen tetroxide is used as the nitrating agent, the yields are markedly improved by the presence of aluminum or ferric halides (367). Even a substance such as fluorobenzene or iodobenzene gives 80 to 90 per cent of the theoretical yields (364).

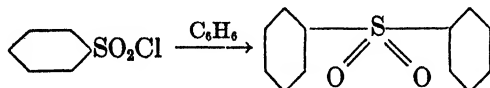


The products contain a preponderance of the para-isomer.

Ethyl nitrate will also introduce the nitro group (28). With benzene and aluminum chloride, nitrobenzene results; with toluene, *o*- and *p*-nitrotoluene are the products. The *p*-isomer forms 80 per cent of the product.

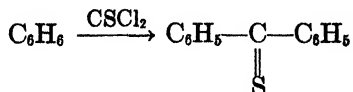


(c) The synthesis of sulfones. It is to be expected that the sulfonyl chlorides will generally introduce a sulfone group in the Friedel-Crafts acylations. In fact, the reaction is generally applicable to sulfonyl chlorides and to aromatic nuclei which undergo acylation (35, 308, 312, 452, 313).

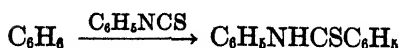
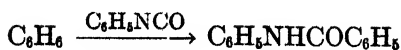


The alkyl- or halogeno-benzenes yield generally the para-substituted sulfones. Here again the so-called "highly negative" groups, such as carboxyl, formyl, keto, and nitro, inhibit reaction when they occur alone in the benzene nucleus (see the section on activating groups, p. 370).

(d) Formation of thioketones, thioanilides, and dithiocarboxylic acids. Certain sulfur-containing substances, such as thiophosgene, behave as do their oxygen-containing counterparts in the Friedel-Crafts reaction. Thiophosgene yields with benzene derivatives and aluminum chloride the corresponding thioketones (135).



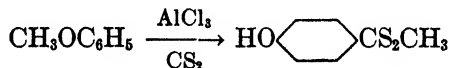
Thioanilides may be formed by reaction of benzene with phenyl isothiocyanate and aluminum chloride (125, 354), in a manner analogous to that used for the oxygen-containing phenyl isocyanate.



In connection with doubly bound nitrogen, it is of note that azobenzene does not give triphenylhydrazine, as might be expected. Instead it undergoes a reduction and rearrangement to yield benzidine.

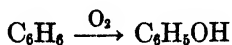


Even carbon disulfide, widely used as a solvent for the Friedel-Crafts reaction, will actually enter the condensations. The easily substituted types, such as the phenol ethers, yield an interesting product with carbon disulfide and aluminum chloride (212). Anisole, for example, yields *p*-dithiocarbomethoxyphenol. It has been suggested that the alkyl group is apparently cleaved from the ether linkage and combined with halogen of the aluminum halide to form an alkyl halide, which reacts with the carbon disulfide to form methyldithiocarbonic acid chloride,  $\text{ClCS}_2\text{CH}_3$ . This latter compound then acylates the phenol in a normal manner. The net reaction is

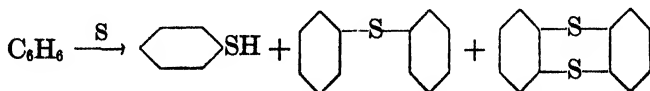


Since gaseous methyl chloride will actually enter into this reaction without alkylating the nucleus, the above mechanism seems logical (144). Many of the sometimes troublesome red residues in the Friedel-Crafts alkylations are these dithiocarboxy compounds. The dithiocarbomethoxy esters have also been observed in the alkylation of the furan nucleus (144).

(e) The introduction of oxygen, sulfur, selenium, arsenic, and phosphorus. It is interesting to note that oxygen may be introduced into a nucleus as inert as benzene by means of the Friedel-Crafts reaction. It is an established fact that when oxygen is not excluded from Friedel-Crafts syntheses, one of the complicating reactions is the introduction of oxygen into the nucleus to form phenolic substances (443, 206).



Sulfur behaves in a manner similar to oxygen to form thiophenol (43), diphenyl sulfide, and thianthrene (345).

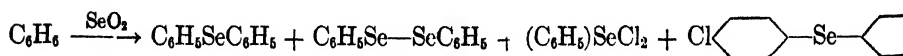


Sulfur monochloride yields diphenyl sulfide, diphenyl persulfide, and sulfur (43) when condensed with benzene by means of aluminum chloride.



Toluene undergoes these reactions with greater ease than benzene, while chlorobenzene does not yield a sulfur-containing product. If the starting substances are thiophenols, or diphenyl sulfide with aluminum chloride, the products of the reaction are essentially the same as if benzene and sulfur were used (81, 82).

As might be expected, selenium behaves very much as does sulfur in the Friedel-Crafts syntheses. Benzene, selenium dioxide, and aluminum chloride yield, upon reaction, diphenyl selenide and diphenyl perselenide as the essential products (250). Smaller quantities of diphenylselenium dichloride, and di-*p*-chlorophenyl selenide were isolated. It is interesting to note the chlorination of the benzene ring.



Toluene behaves in a manner analogous to benzene (71), to yield as the main product tri-*p*-tolylselenium chloride.

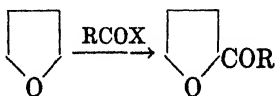
Certain arsines have also been synthesized by this method. Aluminum chloride, benzene, and methylphenylarsine chloride react to give methyl-diphenylarsine (50). The corresponding *p*-tolyl compound may be obtained from toluene (199).

Similarly, phosphorus may be introduced into the benzene nucleus from phosphorus trichloride (231, 122) by aluminum chloride.

### B. The acylation of heterocyclic compounds

(a) The oxygen-containing rings. Partly as a result of the sensitivity of the oxygen-containing rings, coupled with the lack of demand for the products, there is no extensive literature on the oxygen-containing heterocyclic rings in regard to acylation by the Friedel-Crafts reaction. The principal nucleus of this nature that has been studied is that of furan.

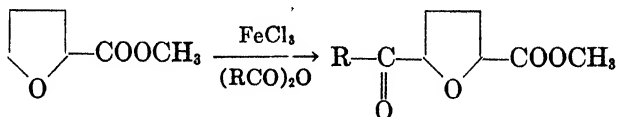
As was pointed out above, unsubstituted furan has not been alkylated. To be contrasted with this is its ready acylation in good yields. Furan will undergo the Friedel-Crafts reaction to yield ketones or an aldehyde. If furan is treated with aluminum chloride and an acid chloride in a suitable solvent, ketones may be obtained in good yields (144, 347).



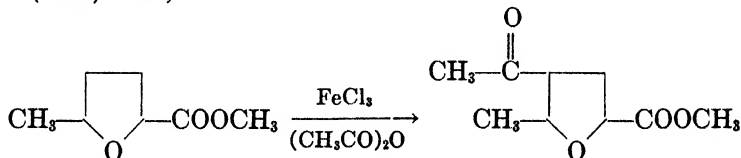
The general observation that the entering group goes to the usual position, that is, either 2 or 5 (143a), is valid in every case of furan acylation, regardless of the nature of the entering group (144).

Furan also acylates easily with anhydrides to yield ketones (145b, 144).

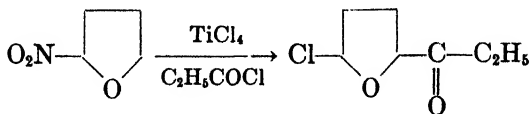
The substituted furans may be acylated to give substituted furyl ketones. 2-Methylfuran is acylated in the 5-position by means of an acid chloride (347) or an anhydride to yield a ketone (145b). Methyl furoate will acylate in the 5-position to yield the corresponding ketone. Strangely enough neither an acid chloride nor an acid anhydride would acylate methyl-2-furoate with aluminum chloride as the condensing agent. In contrast to this latter fact, ferric or stannic chloride acylates methyl 2-furoate with relative ease (144).



When a methyl group occupies the 5-position, as in methyl 2-methyl-5-furoate, the entering acyl group goes to the 4-position (145). In the event the 5-position is occupied by a nitro group or bromine atom, no reaction occurs (144a, 145b).

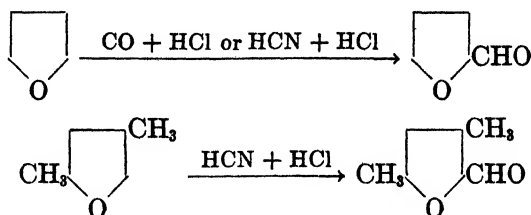


Although certain negatively substituted furans will undergo the Friedel-Crafts acylations, as is shown above and as is true with 2-bromofuran, so far all attempts to acylate a nitrofuran have been futile (54). 2-Nitrofuran generally decomposes badly in attempts to acylate it. However, titanium tetrachloride produces an interesting reaction in which the nitro group is replaced by a chlorine atom and a keto group is introduced into the ring (145b).



Stannic, ferric, aluminum, and titanium chlorides may be used to acylate furan. This is the suggested order of their decreasing activity for the acylation of the furan nucleus (54). For a further discussion see the section on condensing agents (p. 374).

The introduction of formyl groups by the use of either the hypothetical formyl chloride or formimine chloride into either unsubstituted or alkylated furan yields the corresponding 2-furfural (346, 349, 348).

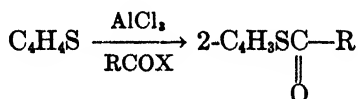


So far it has not been possible to introduce the formyl group into the  $\beta$ -position or into negatively substituted furans (348, 54).

The relative ease with which furan undergoes the Friedel-Crafts reaction is emphasized by the fact that benzene may be used as the solvent for acylations (144, 347). Benzene is a particularly good solvent if stannic chloride is the condensing agent.

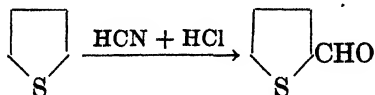
Unfortunately, very few stable hydroxyfurans are known. This has prevented an application of the Fries rearrangement to the furan nucleus. However, when phenols and furoyl chloride or phenolic esters of furoic acid are treated with aluminum chloride a Fries transformation occurs (143).

(b) The sulfur-containing rings. Thiophene, like other aromatic types, will undergo acylation. Acid halides with aluminum chloride may be used to obtain excellent yields of the 2-substituted thiophene (276, 368).

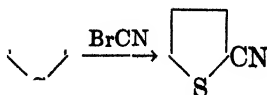


Besides aluminum, stannic (408, 148), or titanium chlorides, the condensing agent may be phosphorus pentoxide. The reaction occurs with the phosphorus pentoxide at elevated temperature to give good yields of ketones (416, 419).

By using hydrogen cyanide and hydrogen chloride with aluminum chloride, a formyl group may be introduced into thiophene (348).

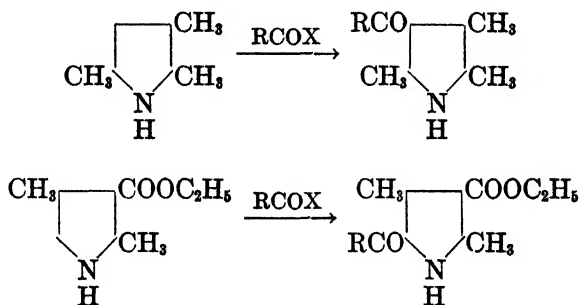


The nitrile group has been introduced into thiophene by means of the Friedel-Crafts reaction. This is analogous to the corresponding reaction with benzene (417, 123).

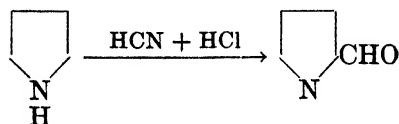


(c) Nitrogen-containing rings. Generally the nitrogen-containing rings are peculiarly resistant to the Friedel-Crafts substitutions. Apparently the only unsubstituted nitrogen ring which has been acylated by the Friedel-Crafts method is pyrrole. In fact, pyrrole will acylate without a catalyst when it is refluxed with acetic anhydride (370). It was at first suspected that this product was the *N*-acetylpyrrole, but it was later shown to be 2-acetylpyrrole (56a).

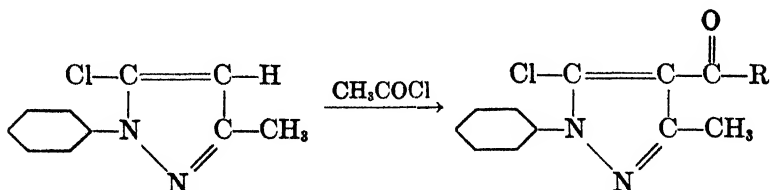
Substituted pyrroles may be acylated in the normal Friedel-Crafts manner. The entering keto group goes to an open 2- or 5-position. If both of these positions are blocked, then the keto group enters the available position (111).



The aldehyde group is introduced with great ease, using hydrogen cyanide and hydrogen chloride (346, 112).

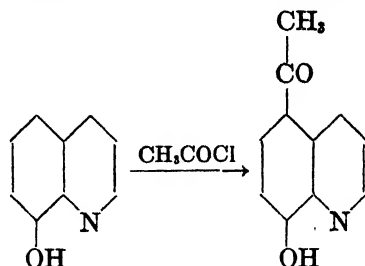


The information on the acylation of the pyrazoles is exceedingly meagre. 1-Phenyl-3-methyl-5-chloropyrazole will acylate to yield the 4-acyl derivatives (272).

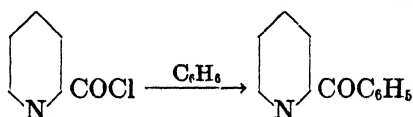




With quinoline only an isolated case of acylation has been reported. In this instance it was found possible to introduce the acetyl group into the 5-position if an hydroxyl group occupied the 8-position (256, 256a).

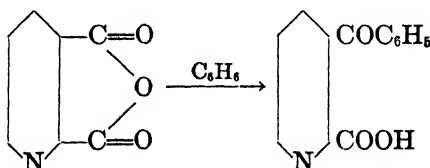


Although the following cases are not examples of the acylation of nitrogen-containing rings, these rings enter into the reaction, yielding acylated substances of such a nature that the product is identical with the product that would be obtained if the rings underwent acylation. For example, it has not been found possible to acylate pyridine. However, acid derivatives of pyridine will acylate benzene (157). Picolinic acid chloride yields with benzene and aluminum chloride the corresponding  $\alpha$ -benzoylpyridine.

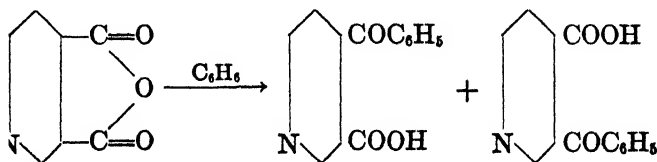


Nicotinic acid halides behave in a similar manner (219b).

Quinolinic anhydride reacts with benzene as does phthalic anhydride to yield  $\beta$ -benzoylpicolinic acid (219, 208, 19). The benzene rings reacts with the carbonyl furthest removed from the nitrogen atom.

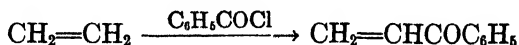


Cinchomeric acid anhydride behaves in a similar manner to give the isomeric substances,  $\beta$ -benzoylisonicotinic acid and  $\gamma$ -benzoylnicotinic acid (219a).



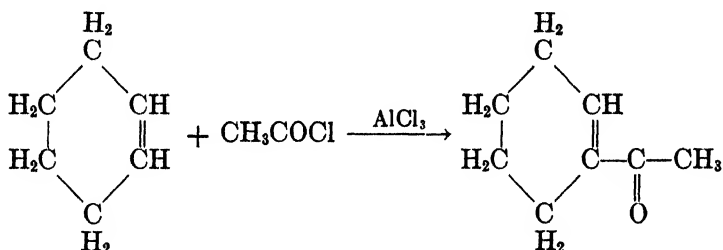
### C. The acylation of aliphatic types

(a) Unsaturated compounds. If benzene is considered an unsaturated hydrocarbon, it is not surprising that some unsaturated hydrocarbons acylate by the Friedel-Crafts method. The simplest unsaturated hydrocarbon, ethylene, acylates by means of benzoyl chloride to produce vinyl phenyl ketone in 25 per cent yields (305).



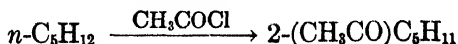
Other open chain unsaturated hydrocarbons behave in a similar fashion. Propylene, the butylenes, trimethylethylene, hexylene, and heptylene yield ketones with acyl halides (232).

The cyclic olefins behave in the expected manner, to yield ketones. For example, cyclohexene yields methyl cyclohexenyl ketone when condensed with acetyl chloride and aluminum chloride (449).

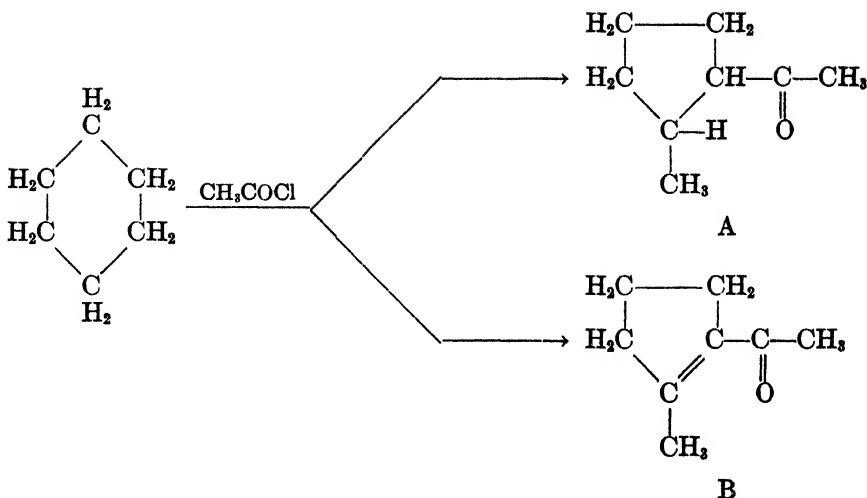


Of the more complex unsaturated substances, cholesterol, ergosterol, and dicyclopentadiene give no acylated products (448), while camphene does give a ketone (247, 450).

(b) Saturated substances. The saturated hydrocarbons undergo the Friedel-Crafts acylation to yield saturated and unsaturated ketones. The higher members of the paraffins undergo this replacement, while methane, ethane, and propane do not (194, 295). Thus, pentane yields 2-acetyl-pentane when condensed with acetyl chloride in the presence of

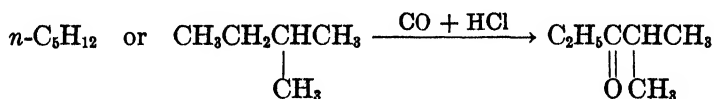


aluminum halide. Cyclohexane, on the other hand, rearranges as it acylates to yield with acetyl chloride, for example, 1-methyl-2-acetylcyclopentane (A) and 1-methyl-2-acetylcyclopentene-1 (B) (431, 193, 462, 297).



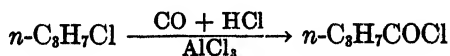
The relative quantities of A and B produced depend on the purity of the aluminum chloride. Very pure, absolutely anhydrous aluminum chloride yields A in a quite pure form, while moisture- or oxygen-containing substances (295), as well as the presence of ferric chloride (262), may produce pure B.

Attempts to carry out the so-called Gattermann-Koch synthesis of aldehydes led to interesting but anomalous results. *n*-Pentane and 2-methylbutane with carbon monoxide, hydrogen chloride, and aluminum chloride under 150 atmospheres pressure gave ethyl isopropyl ketone (194). Here we have a novel reaction which, in essence, cleaves an aliphatic chain, introduces a carbonyl group, and then recombines the fragments. There was also isolated a small quantity of  $\alpha$ -methylvaleric acid,



which indicates that the so-called normal course of the reaction was followed in part with subsequent oxidation.

Another observation, as interesting as the above reaction, was made on the treatment of alkyl halides with carbon monoxide and aluminum chloride. Acid chlorides were produced: *n*-propyl chloride, for example, gave *n*-butyryl chloride (194).



A patent covers a similar reaction (90).

## IV. ORIENTATION AND RELIABILITY

In some cases the Friedel-Crafts reactions are reliable, but in all cases of the synthesis of a new product by this reaction it is advisable to determine the structure and orientation by other means. Thus for proof of structure, the transformations effected by active metal halides are generally invalid.

As gloomy a picture as this may be, the Friedel-Crafts syntheses remain, as is well known, most valuable reactions for laboratory and industry. A note of warning is in order, however, since unpredictable and unparalleled results are constantly occurring.

It may be generally said that alkylations are more variable and unreliable than acylations, but it must be remembered that the reliability of the reaction depends on several factors. Foremost among these contributing effects are the nature and purity of the catalyst, the solvent, the alkylating or acylating reagent, the substance undergoing reaction, the foreign bodies present, and the temperature.

In spite of the lack of uniform behavior in these reactions, there are certain general rules of behavior that may be observed. First, substituents already present in a nucleus generally direct normally as they would for other substitution reactions, such as nitration and halogenation, although this is not always true. Secondly, alkyl halides undergo rearrangement during reaction to give, usually, the most highly branched alkyl groups. This makes it virtually impossible to introduce an alkyl group with a normal chain of more than two carbon atoms.

The question of the orientation is a vital one. However, a highly detailed discussion of the orienting influences in Friedel-Crafts syntheses would take us far afield. Table 1 lists the various groups, their directing influences, and the pertinent references.

No discussion of the general reliability of the Friedel-Crafts syntheses is complete without mentioning some of the unusual conditions that affect the yield and the nature of the product. The ease with which alkyl halides undergo rearrangement to yield more highly branched alkyl groups is of paramount importance. Alkyl halides rearrange under a variety of conditions. Heat (271, 108) or catalysts (392a, 144, 168) will effect this rearrangement. Thus it is to be expected that in the Friedel-Crafts alkylations the normal and slightly branched chains tend to yield the highly branched alkyl groups. For example, *n*-butyl chloride rearranges to yield secondary and tertiary (144) groups.

A discrepancy in the rules of orientation is noted with the methyl group, which will at times direct in part to the meta position and not to the ortho position. This seems to be particularly true when the entering group is

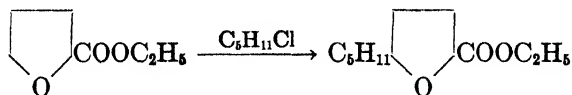
highly branched, such as *tert*-butyl (392a) or isopropyl (236). It is to be remembered that with lower alkyl groups the benzene ring may be completely alkylated to produce hexaalkylbenzenes (5, 11).

Besides the rearrangement, the alkyl group may be cleaved to yield short alkyl groups, that is, a long chain alkyl halide, for instance, amyl or hexyl, may yield on reaction a butyl group. This appears to depend on

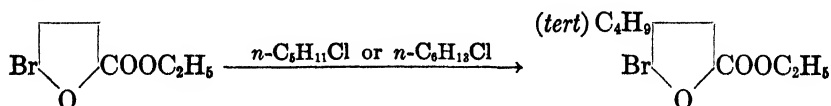
TABLE 1  
*Directing influence of various groups in benzene*

GROUPS	ORIENTATION	REFERENCE
Hydroxyl . . . . .	<i>o, p</i>	(277, 117)
Alkoxy . . . . .	<i>o, p</i>	(257)
Phenoxy . . . . .	<i>o, p</i>	(350)
Methyl . . . . .	<i>o, p</i>	(236, 197, 176, 453)
Chloro . . . . .	<i>o, p</i>	(156)
Bromo . . . . .	<i>o, p</i>	(156)
Amino . . . . .	<i>o, p</i>	(67, 410, 274a)
Chloromethyl . . . . .	<i>o, p</i>	(362)
Diphenyl . . . . .	<i>o, p</i>	(161, 378)
Benzyl . . . . .	<i>o, p</i>	(343, 445)
Formyl . . . . .	<i>m</i>	(144a, 147, 145c)
Carboxyl . . . . .	<i>m</i>	(144, 20)
Nitro . . . . .	<i>m</i>	(422)
Dichloromethyl . . . . .	<i>m</i>	(445)
Keto . . . . .	<i>m</i>	(257)

the substance undergoing reaction. For example, ethyl 2-furoate gave with the amyl or hexyl halides the expected alkylated substances (144, 147).



But when ethyl 5-bromo-2-furoate was substituted for ethyl 2-furoate, thus forcing the entering substituent into the 4-position, *all alkyl halides with more than four carbon atoms gave only ethyl 5-bromo-4-*tert*-butyl-2-furoate* (145c).



Even *n*-octadecyl bromide cleaved to yield the above *tert*-butyl ester (147a).

A similar observation has been made in alkylation by olefins. Diam-

ylene and benzene yield butyl-, amyl- and hexyl-benzenes (428a), and not a decylbenzene.

These reactions are not particularly surprising when it is reflected that aluminum chloride is an excellent agent for "cracking" paraffins (251, 252, 253). The action of the aluminum chloride generally takes a course that yields a smaller molecule than the one contained in the initial reactant. The lighter and gaseous members of the hydrocarbons may be formed (95, 98), as well as certain higher hydrocarbons.

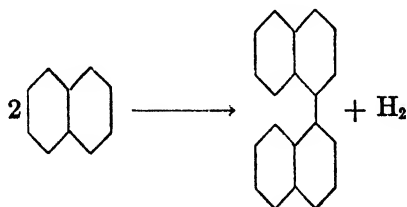
Attention must also be given to the side reactions which the compound undergoing substitution may suffer. In general these reactions are of two forms, disproportionation and cleavage of chains and rings.

Under disproportionation come the reactions that couple the nuclei undergoing substitution and that result in such changes as the removal and wandering of halogens, the movement of alkyl groups in alkylated substances, and the production of tars and gums of an undefinable nature. These reactions take place under anhydrous conditions in an inert atmosphere. If oxygen, moisture, or carbon dioxide be admitted, then the reactions characteristic of these substances will occur.

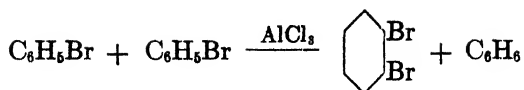
Benzene, for example, with aluminum chloride yields a minute quantity of diphenyl (206). However, with other hydrocarbon types, this reaction is prevalent. This is the so-called Scholl reaction and is fundamentally an elimination of a molecule of hydrogen to give a coupled product (379, 380, 381). Although the heavier aromatic types such as naphthalene and anthracene give better yields of coupled products, the simple aromatic nuclei undergo a similar coupling (64).

Even the cycloparaffins tend to couple with evolution of hydrogen as the aromatic nuclei do (296, 293, 206).

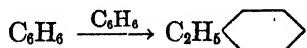
The liberated hydrogen may cause reductions of the other reactants. For example, the acid halides may be reduced to aldehydes (296).



Under the influence of aluminum chloride, even the halogens attached to the aromatic nuclei may migrate in the ring or to another ring (64, 89, 226).



As might be expected the cleavage reactions take a variety of courses. Besides those cleavage reactions already mentioned, the aromatic rings may undergo complete decomposition to form fragments that undergo simultaneous reduction to yield alkyl groups that will enter the remaining nuclei. This process has been pictorially described as "destructive alkylation" (206). The over-all reaction is represented simply:—



Even methyl radicals of methoxyl groups may be eliminated by an active metal halide (327). However, the methyl radical does not tend to rearrange to the nucleus under these conditions (337). Although these reactions take place in the average Friedel-Crafts reaction, they are usually found to produce a more or less small fraction of the total products, depending largely on the conditions. Generally, high temperatures, high concentration of condensing agent, and a long reaction time favor the side reactions, although these same conditions may be required to effect the condensation. It is worthy of note here that in carbon disulfide these side reactions appear to be materially diminished. It has been shown that methyl groups do not migrate or rearrange when the solvent is carbon disulfide (358).

Although these reactions do not represent the entire picture of the side reactions, they are typically representative and give an idea of the complexity that may be attained in the Friedel-Crafts syntheses.

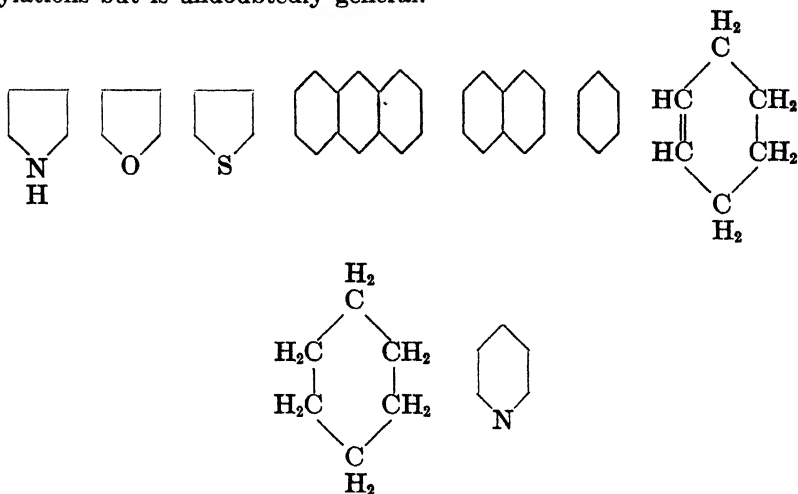
#### V. ACTIVATING AND INHIBITING GROUPS

It is in line with observations on orientation in the Friedel-Crafts syntheses to note that just as in other substitution reactions the presence of substituents may increase or decrease the ease of further substitution into the nucleus.

The Friedel-Crafts reactions are definitely substitution reactions. As such they are not violent reactions nor are they necessarily, as a class, vigorous. In fact the introduction of alkyl and acyl groups may be made a mild reaction by controlling the conditions. The reactions *are* unreliable sometimes and even decompose the reactants. But these are eccentricities and are not properly viewed as an aspect of being violent or unduly vigorous. Many compounds that undergo nitration, halogenation, or sulfonation with comparative ease, either react with difficulty or entirely fail to substitute in a Friedel-Crafts reaction. Even benzene itself is

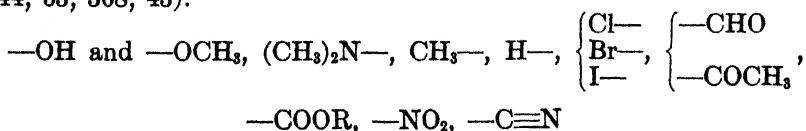
resistant to *some* types of Friedel-Crafts substitutions, such as the Gattermann or Gattermann-Koch modifications.

Generally, unsubstituted rings will undergo the Friedel-Crafts substitutions. These appear to fall in an order that may be discerned from the various researches. Some have been compared directly. Others must be placed by a comparison of the work of different investigators (144, 346, 347, 348, 53, 54). On the basis of a general review, the unsubstituted rings arrange themselves from left to right, in the order of their decreasing ease of substitution in a series that is not exact for all alkylations and acylations but is undoubtedly general.



Pyrrole is given the most active position here with the understanding that the reactions probably proceed through the intermediate formation of *N*-alkyl or *N*-acyl compounds which rearrange. Because of this activity of the =NH group, perhaps pyrrole should not be included in the series.

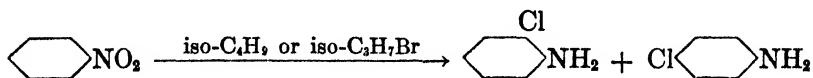
For the substituted types, it is easy to point out the compounds which will and will not undergo the Friedel-Crafts syntheses, but it is more difficult to arrange the groups in an *order* of activity, since few direct comparisons have been made. Nevertheless, judging from the available material and from comparisons from scattered sources, the following order is approximately correct. It is certain that the general scheme and classification is correct for a decreasing activity from left to right. Some of the groups may, under varying conditions, assume a slightly altered order (144, 53, 308, 43).





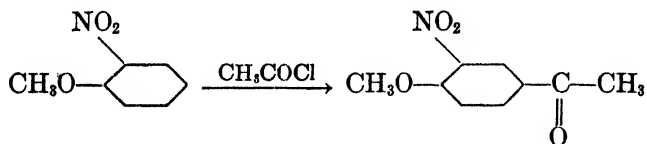
In general an increasing so-called electronegativity (217a) of the group increases the difficulty of substitution. So far no successful attempts to alkylate or acylate nitriles have been reported.

The fact that nitrobenzene is used as a solvent for many Friedel-Crafts transformations indicates its inert nature in regard to substitutions in alkylation or acylation. All attempts to introduce an alkyl or acyl group into nitrobenzene have been futile. On prolonged reaction in attempting to alkylate nitrobenzene, reduction ensues and amines result. After thirty days reaction at room temperature, or in a shorter time at elevated temperature, isopropyl or isobutyl bromides with aluminum chloride and nitrobenzene give small quantities of *o*- and *p*-chloroaniline (145b) with a large fraction of unchanged nitrobenzene.



These products may be considered anomalous, although both reduction of the nitro group (87, 222) and halogenation of the benzene nucleus (250, 159) have been observed separately. This work emphasizes the desirability of careful isolations in the Friedel-Crafts transformations.

If one of the highly activating groups such as methoxyl is present, the nitro group no longer prohibits reaction (422).



The carboxyl group which normally prohibits reaction (144, 406, 20) will not interfere if a group such as methoxyl is present in the ring. Thus methyl anisate alkylates with ease, while methyl benzoate does not.

For ketones, the presence of alkyl groups (270, 137) is sufficient to cause activation of such a nature that substitution will occur, notwithstanding the fact that the keto group markedly inhibits reaction (124a) in such a way that only mono keto substances may be obtained when unsubstituted benzene is acylated. That is, only one acetyl or benzoyl group enters benzene, while two or more will enter durene (270) and hydroxy- or alkoxy-benzenes (257, 357a, 291).

Similarly the formyl group inhibits reaction. However, it has been found possible to alkylate benzaldehyde in exceedingly low yields (147). Here again the alkoxy group is of sufficient activating influence to cause anisaldehyde to alkylate smoothly (144a).

Numerous observations have been made that the halogens deter substitution in alkylation or acylation. Thus the difficulty in acylating or alkylating is increased in a halogenobenzene (42, 43), although the exact order of interference for the halogens is not established definitely. In this connection, it has been shown that for sulfone formation chlorobenzene is more resistant than bromobenzene (308).

Besides the examples mentioned above there are many cases in which methyl (259, 391, 98, 172), amino (274, 410), and methoxyl (410, 256, 256a, 134) activate the nucleus so that substitution occurs with increased ease.

## VI. SOLVENTS

Although the actual technique of the Friedel-Crafts syntheses cannot be dealt with in detail here, a word must be said concerning the solvents used, since they vitally affect the reactions. Perhaps the most general practice is to use as the solvent an excess of the hydrocarbon or substituted hydrocarbon that is undergoing substitution. Obviously unless this reactant is liquid under the conditions of the reaction, it cannot be used. Thus, for the substitution of alkyl and acyl groups into benzene, the latter compound is almost invariably the solvent. Although this practice yields ketones effectively, it is not generally a desirable method for alkylation, where a definite product and high yield are the major interests. Not only is benzene used in this way, but other liquid reactants such as toluene and chloro- or bromo-benzene may be used (308, 160). In some cases a substance like carbon tetrachloride may be used if it is one of the reactants (353).

Obviously there are often reasons why one of the reactants cannot be used as the solvent. Sometimes no solvent is necessary; the reactants, even though solid, are made to react directly by grinding together molecular quantities and fusing the mass. In many cases this affords excellent results (284, 161, 176, 354).

When it is desired to eliminate one of the reactants as the solvent, an inert solvent may be used. Generally, this is either carbon disulfide or a petroleum ether. Carbon disulfide appears to have a specific action on the Friedel-Crafts syntheses, tending to prevent migration of groups (358). It is generally an excellent solvent for a variety of alkylations (144, 343) or acylations (302, 257, 308). In some cases, carbon disulfide may influence the reaction markedly and in a few cases actually reduce the yield (278) or control the velocity of reaction (353). But it remains as one of the best general solvents for the Friedel-Crafts syntheses.

The exact nature of the rôle that the solvent plays here is uncertain. As has been so well pointed out (277a, 184), the action of the solvent is at

times subtle and deep-seated and far more significant than one would expect of a simple medium for reaction.

Petroleum ethers exhibit properties similar to those of carbon disulfide when used as solvents (358, 202, 103, 81).

When highly reactive compounds are used, or when mild condensing agents are employed, solvents such as *o*-dichlorobenzene (160), acetylene tetrachloride (350), benzene (144, 347, 178), and diethyl ether (347, 170, 171) may be used. Under these conditions the alkylation or acylation of the substance in question must be so rapid that the solvent, though reactive under some conditions, does not have an opportunity to react. For example, when benzene is used as a solvent for the acylation of furan by acetic anhydride and stannic chloride, the major product is the acylated furan (347, 144), although benzene will undergo slow acylation under these conditions. Also, anthracene may be acylated in benzene solution by phthalic anhydride and aluminum chloride (178). This is to be compared with the quantitative yield of ketone that may be obtained from benzene, aluminum chloride, and phthalic anhydride (359) when the anthracene is absent.

Nitrobenzene finds its use as a solvent not only as a result of its high boiling point and excellent solvent nature, but largely because of the fact that it forms complexes with the metal halide, thereby materially reducing its activity. This complex formation lessens the charring and disproportionating action of the aluminum chloride, thereby making the introduction of alkyl and acyl groups essentially a mild reaction (308, 355, 385, 256) applicable to sensitive types like phenols, amines, benzyl halides, or quinolines (308, 355, 383, 256).

## VII. THE CONDENSING AGENTS

Generally, the mention of the Friedel-Crafts reactions immediately calls to mind aluminum chloride. This is perfectly reasonable, since aluminum chloride was the first well-described condensing agent and the one that is in by far the most general use, although no less than fifteen different substances have been used in the various Friedel-Crafts reactions as condensing agents. The resublimed aluminum chloride is obtainable commercially in a state of high purity and at a low cost per pound (158). When all factors are considered, there is little doubt that aluminum chloride is the best general catalyst for the Friedel-Crafts syntheses. For the alkylation or acylation of substances that undergo replacement with ease, other condensing agents may be found superior to aluminum chloride. Regardless of the pseudospecific action of certain condensing agents, they all have essential characteristics in common. Usually they are metal halides. Under all circumstances they are essentially anhydrous. Al-

though we have limited ourselves here to discussions of alkylations and acylations by active metal halides, there are a few special cases where closely related catalysts are used, and these are not metallic halides. It

TABLE 2  
*Condensing agents*

SUBSTANCE	TYPE OF REACTION	REFERENCES
$\text{AlCl}_3$ .. . . .	Acylations and alkylations	(144, 294, 64, 154, 298)
$\text{AlBr}_3$ . . . . .	Acylations and alkylations	(64)
$\text{SbCl}_5$ . . . . .	Acylations	(60a)
$\text{SbCl}_3$ . . . . .	Acylations	(264)
$\text{BF}_3$ . . . . .	Alkylations	(405, 187, 72)
$\text{FeCl}_3$ . . . . .	Acylations and alkylations	(444, 144, 298, 353, 260)
$\text{SnCl}_4$ . . . . .	Acylations and alkylations	(406, 148, 76)
$\text{NaCl} \cdot \text{AlCl}_3$ . . .	Alkylations	(122)
$\text{TiCl}_3$ . . . . .	Acylations and alkylations	(214)
$\text{TiCl}_4$ . . . . .	Acylations and alkylations	(213, 408)
$\text{ZrCl}_4$ . . . . .	Acylations and alkylations	(233)
$\text{ZnCl}_2$ . . . . .	Acylations and alkylations	(444, 134, 412, 138)
$\text{Hg} \cdot \text{Al}$ . . . . .	Acylations and alkylations	(130, 345, 34)

TABLE 3  
*Condensing agents not generally applicable*

SUBSTANCE	TYPE OF REACTION	REFERENCES
$\text{ClCH}_2\text{COOH}$ . . . . .	Acylations	(730)
$\text{HgCl}_2$ . . . . .	Acylations	(53)
$\text{P}_2\text{O}_5$ . . . . .	Acylations	(419)

TABLE 4  
*Substances which have given no indication of catalytic activity*

SUBSTANCE	TYPE OF REACTION	REFERENCES
$\text{PbCl}_2$ . . . . .	Acylations	(53)
$\text{CuCl}_2$ . . . . .	Alkylations	(122)
$\text{CoCl}_2$ . . . . .	Alkylations	(122)
$\text{MgCl}_2$ . . . . .	Acylations	(122)
$\text{SiCl}_4$ . . . . .	Acylations	(53)
$\text{CaCl}_2$ . . . . .	Acylations	(53)
$\text{CrCl}_3$ . . . . .	Acylations	(131)

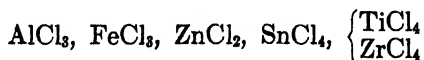
is found that the anhydrous substances listed in table 2 catalyze some of the Friedel-Crafts reactions. While under certain conditions the substances listed in table 3 may be used as condensing agents, they have not been shown to be generally applicable. The substances listed in table 4

have given no indication of catalytic activity. It is to be noted that beryllium chloride is essentially inactive (444).

There are a few general characteristics which the efficient condensing agents (table 2) have in common. With the exception of iron, they arise from the elements that are centrally located in the periodic table. All the elements are more or less amphoteric and form highly hygroscopic anhydrous halides. These anhydrous halides are essentially non-polar in the anhydrous form and possess typically quite low boiling points (395, 207, 21), with the exception of zinc chloride (m.p. 365°C. b.p. 730°C.). However, all substances that show these properties are not active catalysts in the Friedel-Crafts condensations. For example, the carbon and silicon tetrahalides do not catalyze the elimination of hydrogen halide.

Thus the nature of the catalyst appears to depend not only on the polarity of the halogen bonds, but fundamentally on the complex electronic structure of the central atom. The problem forms a phase of the Friedel-Crafts reactions that is greatly in need of elucidation. It appears from present knowledge that one essential feature that all of the condensing agents must have is a great facility for forming a highly active complex with one or both reactants.

It is not to be inferred that the condensing agents must necessarily be usable interchangeably. It is sometimes true that these catalysts may be substituted for each other, but many of them show a definite activity which limits their use to certain nuclei or substituted rings. For example, while aluminum chloride will introduce groups into benzene, thiophene, furan, or the substituted benzenes, stannic chloride fails to produce a reaction with certain substances such as chlorobenzene. Stannic chloride, however, does activate a reaction slowly with benzene (53), and it produces a reaction easily with furan (144) or thiophene (148). Similar observations have been made with titanium tetrachloride (408), zirconium tetrachloride (233), ferric chloride (131, 353), zinc chloride (131), and others, so that it is possible to formulate a series of general activity. It must be realized, however, that conditions of comparison were not always exactly the same. But there is sufficient cumulative evidence as to the commonly used reagents to show that the following decreasing order of activity is generally valid.



The other condensing agents have not been sufficiently studied to warrant placing them in the series, but all appear to be less active than stannic chloride. Thus from this series it is seen that it is possible to select a condensing agent so that preferential substitution will occur. For example,

by using stannic, titanium, or zirconium halides it is possible for some active substances such as anisole, thiophene (407, 408), or furan (144, 347), to be alkylated or acylated in benzene solution.

One factor that vitally affects the behavior of the condensing agent is the presence of impurities. In fact, traces of various foreign substances markedly alter both the yield and the direction of the reaction. A trace of moisture, for example, will tend to promote the removal of hydrogen from aliphatic substances (295), or it may increase the disproportionating and rearranging tendency of the catalyst (294). Water, however, is not the only substance that will produce this behavior. Other oxygen-containing substances besides water, such as phosphorus oxychloride, nitrobenzene, benzophenone, or acetone, behave in a similar manner (295).

Occasionally substances may be found that increase reaction yields when used in conjunction with the regular condensing agent. In the introduction of the formyl group by carbon monoxide and hydrogen chloride, using aluminum chloride as the condensing agent, it has been found that cuprous chloride markedly increases the yield (139). More recently it has been observed that mercury will influence the alkylation of benzene by vinyl chloride, changing the course of the reaction to inhibit the entrance of more than one benzene nucleus (75). In acylating benzene by organic acids in the presence of aluminum chloride, phosphorus trichloride and thionyl chloride increase the yields, while potassium perchlorate decreases the quantity of ketone obtained (157). Ferric chloride, under some conditions, may increase the yield of product in certain Friedel-Crafts reactions (352), when used with aluminum chloride.

The highly specific condensing agents (table 3) are interesting. As has been pointed out, many types of alkylations and acylations may be effected by means of catalysts other than the anhydrous metal halides. These reactions do not belong in the classes of transformations known as the Friedel-Crafts syntheses, but a few warrant mention here.

One of the most interesting is the use of aliphatic chloro acids or chloro anhydrides to act as the condensing agent. Chloroacetic acid, for example, with anisole and an anhydride yields a ketone in 80 to 90 per cent yields on prolonged refluxing, whereas without the chloroacetic acid a yield of only 1.5 per cent is obtained (430).



Chloroacetic acid anhydride behaves in an analogous manner.

Phosphorus pentoxide is useful in the acylation of thiophene by means of anhydrides (419), while mercuric chloride will condense furan with acid chlorides (53). The latter reaction may possibly proceed through the intermediate formation of a chloromercuri compound (143a).

## VIII. MECHANISM OF THE REACTIONS

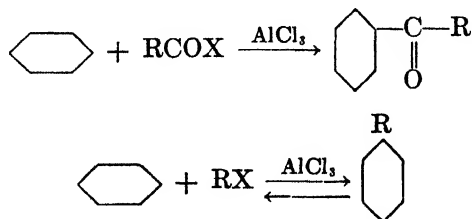
With such a variety of reactions to include in the classes of the Friedel-Crafts syntheses, it is exceedingly difficult to give a concise and yet clear picture of these transformations. To say that the Friedel-Crafts reactions are fundamentally substitution reactions is to present only part of the picture, for the cleavage reactions are as important as the substitution reactions. Indeed, the former frequently accompanies the latter.

It may be that there is not sufficient information available to warrant any attempt to explain fully the mechanism of the Friedel-Crafts syntheses on a single basis. Certainly no one mechanistic view will adequately provide for alkylations and acylations in all of their ramifications. Neither is there evidence that will rationalize the rearranging, disproportionating, reducing, and disrupting or cracking action of metal halides with the smooth introduction of groups into a nucleus. Yet they all appear to be associated with some one property of the condensing agents.

Of course we may adequately explain the entire field of phenomena concerning these reactions if we use such terms as "activating influence," "catalysis," "complexes," "equilibria," etc. Obviously an explanation couched in such broad terms is not fruitful. An explicit interpretation of the mechanism of the Friedel-Crafts syntheses must await further experimental work.

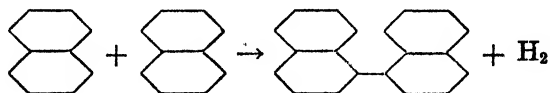
It is necessary to limit the discussion to the action of aluminum halides, and it is unreasonable to expect *all* the condensing agents to behave in the same manner. A glance at the tables of condensing agents raises the question whether or not all of these condensing agents *can* act in the same manner. This is yet to be demonstrated.

Furthermore, it is necessary to limit the discussion to the alkylating and acylating reactants that are halides, that is, alkyl and acyl halides. Here again, there is no evidence to prove that all of the alkylations or the heterogeneous acylations pass through the intermediate formation of halides, although this is a possibly valid view. It is known, however, that many of the alkylating and acylating agents do yield alkyl (262, 18, 447, 243) and acyl (159, 44, 157, 3, 424) halides under influence of aluminum chloride. Thus the two reactions which are to be considered are represented as follows:



where R is alkyl.

There is a definite activating action by the condensing agent. The action appears to affect the nuclear hydrogen and the organic halide. This is brought out by the fact that many types of alkylation (112a, 292) and acylation (68, 430) may be effected in poor yield and at high temperatures without a condensing agent. In these cases, then, the condensing agent only serves to increase the rate of reaction, thereby making it possible to carry out the synthesis at a lower temperature (304). The fact that in the Scholl modification of syntheses by aluminum chloride, hydrogen is actually evolved, gives strong support to the view that in some cases at least the hydrogen undergoes a marked activation by the condensing agent (383, 381, 380).

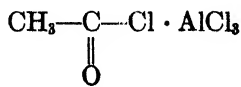
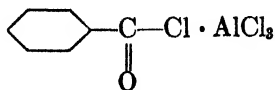


In the "cracking" reactions (16, 428, 443, 292) and in the acylation or alkylation of various nuclei this increased activity of hydrogen is noticed (304, 60, 455, 341).

There appears to be an equal, if not more pronounced, activating influence on the halogen of the alkyl or acyl halide (159, 37, 455).

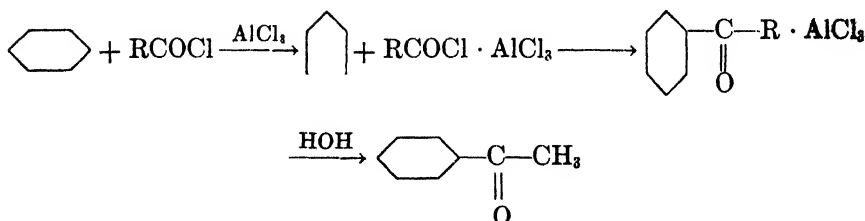
This activating influence of the condensing agent is catalytic. There is no evidence to support the earlier view that an intermediate organoaluminum compound, such as  $\text{C}_6\text{H}_5\text{AlCl}_2$ , forms, followed by reaction with alkyl or acyl halides (373, 387). There are two pieces of information against the theory of intermediate formation of organoaluminum compounds. In the first place, no evidence has ever been established to support the view that such compounds form under the experimental conditions. In the second place, while organoaluminum compounds, such as  $\text{C}_6\text{H}_5\text{AlCl}_2$ , will react with alkyl halides to form alkylbenzenes in poor yields, acyl halides do not yield ketones but condense with themselves (375). This latter fact is to be contrasted with the observation that the Friedel-Crafts ketone synthesis may become quantitative (359, 254).

The catalytic activity of the Friedel-Crafts reaction is promoted through its strong tendency to form complexes with the most diverse types of substances. Alcohols (127), nitriles (283), nitro compounds (334), ethers (326), ketones, and even hydrogen sulfide (429) are some of the substances that form complexes with aluminum halides. In a similar manner aluminum halides form complexes with acyl halides (312, 265, 321, 322).





Thus the reaction for the formation of ketones may be represented by **two** steps.



This course of the reaction has been adequately demonstrated (38, 35, 310).

The reaction appears to be essentially non-reversible in ketone formation (306). However, there are instances in which the removal (14) and migration (61) of keto groups have been reported.

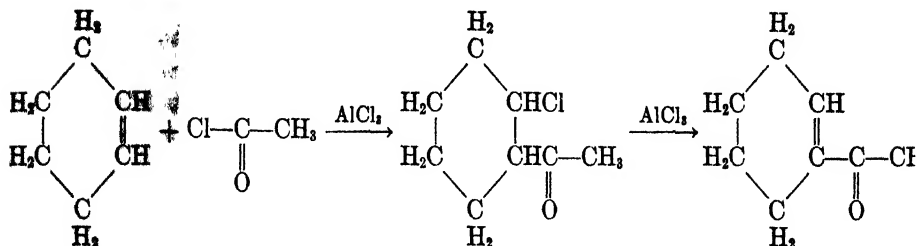
In the cases of acylations, a mole of condensing agent is required for each mole of ketone formed when the acylating agent is an acyl halide (309, 310, 158). When the acylation is carried out using anhydrides, two moles of condensing agent are required for each mole of ketone formed (352, 158).

In spite of the demand for one mole of condensing agent for each mole of ketone formed, the reaction is catalytic. However, the ketone formed in the reaction converts the aluminum chloride to a molecular complex,  $\text{C}_6\text{H}_5\text{COR} \cdot \text{AlCl}_3$  for example, which is not catalytically active (309). A slight excess of the condensing agent increases the velocity of reaction enormously (311). This latter fact emphasizes the catalytic action of the condensing agent.

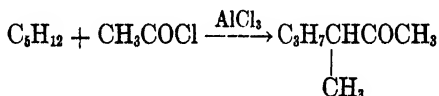
Alkylation is a reversible reaction as shown above (174, 344, 459), and its mechanism differs strikingly from that of acylation. There is no demonstrable complex formation between the aluminum halide and the alkyl halide or benzene, if benzene is being alkylated (268, 212a, 269). However, there is strong evidence that a ternary complex may be formed in which the benzene, aluminum halide, and alkyl halide take part (373, 455, 446). The aluminum halide retains its activity, so that a small quantity of metallic halide may be used to alkylate large quantities of many benzene derivatives. Here a more apparent catalytic relationship exists between the condensing agent and the other reactants (291a, 167, 20).

As to the actual mechanism of the entrance of the group, there is little information. From the fact that aluminum halides will catalyze the addition of alkyl and acyl halides to unsaturated linkages (18, 318, 215, 41), it has been suggested that there is a preliminary addition of alkyl or acyl halide to an unsaturated unit followed by elimination of hydrogen halides

(449). Actually, these addition compounds may be isolated when the substance being acylated is an olefin. The addition compounds eliminate hydrogen halide on further treatment with the condensing agent (449, 232, 421). The following mechanism has been suggested to account for this behavior, although hydrogen chloride may have added to the unsaturated ketone instead.



In what may be opposition to this view, there is the case for saturated hydrocarbons in which paraffins or cycloparaffins undergo acylation (194) to yield saturated ketones.



As is readily apparent, the question of mechanism and catalysis in the Friedel-Crafts syntheses merits a searching experimental study. Elegant work has already been done on the question. Furthermore, the intensely reactive, hygroscopic, and generally insoluble complexes do not lend themselves to an easy study. And, as is true generally with catalytic reactions, there are many uncontrolled contributing factors (184, 185, 277b) that make it rather difficult to inquire into the intricate behavior of the catalysis by active metal halides.

#### IX. SUMMARY

1. As a result of the number of different groups that may be introduced by active metal halides, coupled with the diversity of reactants, solvents, and condensing agents, the expression "Friedel-Crafts *Syntheses*" is preferred to "Friedel-Crafts Reaction."

2. Alkylation is a reversible reaction applicable to practically all types of organic compounds.

3. Acylations are essentially non-reversible and are also applicable to a variety of types of reactants.

4. Rearrangements are prevalent in alkylation, but acylations are more reliable.

5. The orientation of entering groups is essentially that found in other substitution reactions.

6. A variety of condensing agents may be used. Aluminum chloride is apparently the most active.

7. The Friedel-Crafts reaction is catalytic. There is apparently no formation of intermediate organoaluminum substances.

To Mr. Walter Williams, Librarian of Tuskegee Institute, go most sincere thanks for his efforts to obtain obscure references. The chemical libraries at Iowa State College and the Alabama Polytechnical Institute have allowed us to have access to the references not available in the local library.

#### X. REFERENCES

- (1) ADOR AND CRAFTS: Bull. soc. chim. **34**, 531 (1880).
- (2) ADOR AND RILLIET: Ber. **11**, 399 (1878).
- (3) ADRIANOWSKY: J. Russ. Phys. Chem. Soc. **11**, 116 (1879).
- (4) ANSCHUTZ AND FORSTER: Ann. **368**, 89 (1909).
- (5) ANSCHUTZ AND IMMENDORF: Ber. **18**, 556 (1885).
- (6) ASHDOWN: Ind. Eng. Chem. **19**, 1063 (1927).
- (7) BACHMANN AND WISELOGLE: J. Am. Chem. Soc. **56**, 1559 (1934).
- (8) BAEDTKER AND HALSE: Bull. soc. chim. [4] **19**, 444 (1916).
- (9) BAKER: J. Chem. Soc. **1934**, 71.
- (10) BALSOHN: Bull. soc. chim. [2] **31**, 539 (1879).
- (11) BARBOT: Bull. soc. chim. [4] **47**, 1314 (1930).
- (12) BASTET: Chem. Ztg. **37**, 564 (1913).
- (13) BAUER AND TOMA: Ber. **67**, 1135 (1934).
- (14) BAUM AND MEYER: Ber. **28**, 3212 (1895).
- (15) BAUR: Ber. **24**, 2832 (1891).
- (16) BEHIMER: U. S. patent 1,835,748 (1931) to Texas Oil Co.; C.A. **26**, 1111 (1932).
- (17) BERGMANN AND WOLF: J. Am. Chem. Soc. **54**, 1644 (1932).
- (18) BERL AND BITTER: Ber. **57**, 95 (1924).
- (19) BERNTHSEN AND METTEGANG: Ber. **20**, 1208 (1887).
- (20) BIALOBRZESKI AND NENCKI: Ber. **30**, 1776 (1897).
- (21) BILTZ AND VOIGHT: Z. anorg. allgem. Chem. **126**, 39 (1923).
- (22) BODENDORF: J. prakt. Chem. **129**, 340 (1931).
- (23) BODENDORF: J. prakt. Chem. **129**, 337 (1931).
- (24) BODROUX AND TABOURY: Bull. soc. chim. [4] **9**, 595 (1911).
- (25) BODROUX AND TABOURY: Compt. rend. **153**, 349 (1911).
- (26) BODROUX: Ann. chim. [10] **11**, 511 (1929).
- (27) BODROUX AND TABOURY: Bull. soc. chim. [4] **5**, 826 (1910).
- (28) BOEDTKER: Bull. soc. chim. [4] **3**, 726 (1908).
- (29) BOEDTKER AND HALSE: Bull. soc. chim. **19**, 444 (1916).
- (30) BOESEKEN: Rec. trav. chim. **27**, 5 (1908).
- (31) BOESEKEN ET AL.: Rec. trav. chim. **32**, 1 (1913).
- (32) BOESEKEN AND PRINS: Proc. Acad. Sci. Amsterdam **14**, 776 (1911); Chem. Zentr. **1911**, I, 466.
- (33) BOESEKEN AND BASTET: Rec. trav. chim. **32**, 184 (1913).

- (34) BOMSEKEN AND ADLER: *Rec. trav. chim.* **48**, 474 (1929).
- (35) BOMSEKEN AND OCKENBURG: *Rec. trav. chim.* **33**, 317 (1914).
- (36) BOMSEKEN: *Rec. trav. chim.* **30**, 381 (1911).
- (37) BOMSEKEN: *Rec. trav. chim.* **33**, 195 (1914).
- (38) BOMSEKEN: *Rec. trav. chim.* **39**, 622 (1920).
- (39) BOMSEKEN: *Rec. trav. chim.* **19**, 22 (1900).
- (40) BOMSEKEN: *Rec. trav. chim.* **29**, 85 (1910).
- (41) BOMSEKEN: *Rec. trav. chim.* **30**, 148 (1911).
- (42) BOMSEKEN: *Rec. trav. chim.* **27**, 10 (1908).
- (43) BOMSEKEN AND KONIG: *Rec. trav. chim.* **30**, 116 (1911).
- (44) BOMSEKEN AND CLUWEN: *Rec. trav. chim.* **31**, 367 (1912).
- (45) BOWNEAUD: *Bull. soc. chim.* [4] **7**, 776 (1910).
- (46) BOSWELL AND McLAUGHLIN: *Can. J. Research* **1**, 400 (1929).
- (47) V. BRAUN: *Ber.* **64**, 2869 (1931).
- (48) V. BRAUN AND KUHN: *Ber.* **60**, 2557 (1927).
- (49) V. BRAUN AND DEUTSCH: *Ber.* **45**, 1267 (1912).
- (50) BURROWS AND TURNER: *J. Chem. Soc.* **119**, 426 (1921).
- (51) BUSCH AND KNOLL: *Ber.* **60**, 2243 (1927).
- (52) CAILLE: *Compt. rend.* **153**, 393 (1911).
- (53) CALLOWAY: Unpublished observations.
- (54) CALLOWAY: *Iowa State Coll. J. Sci.* **9**, 141 (1934).
- (55) CHOPIN: *Bull. soc. chim.* **35**, 610 (1924).
- (56) CHUGAEV: *J. Russ. Phys. Chem. Soc.* **46**, 1738 (1914); *C.A.* **9**, 2899 (1915).
- (56a) CIAMICIAN AND DENNSTEDT: *Ber.* **16**, 2348 (1883).
- (57) CLAISEN: *Ber.* **54**, 200 (1921).
- (58) CLEMO AND WALTON: *J. Chem. Soc.* **1928**, 723
- (59) COLLET: *Bull. soc. chim.* [3] **17**, 510 (1897).
- (60) COMBES: *Ann. chim.* **12**, 199 (1887).
- (60a) COMSTOCK: *Ann. chim. phys.* **18**, 547 (1896).
- (61) COOK AND CHAMBERS: *J. Am. Chem. Soc.* **43**, 334 (1921).
- (62) COOK AND HEWETT: *J. Chem. Soc.* **1933**, 1408.
- (63) COPISAROW: *J. Chem. Soc.* **111**, 10 (1917).
- (64) COPISAROW AND LONG: *J. Chem. Soc.* **119**, 442 (1921).
- (65) COPISAROW AND LONG: *J. Chem. Soc.* **119**, 1806 (1921).
- (66) COURTOT AND OUPEROFF: *Compt. rend.* **191**, 416 (1930).
- (67) COURTOT AND OUPEROFF: *Compt. rend.* **191**, 214 (1930).
- (68) COX: *Rec. trav. chim.* **50**, 848 (1931).
- (69) CRAFTS: *J. Chem. Soc.* **77**, 993, 1006 (1900).
- (70) CRYER: *Trans. Roy. Soc. Can.* **III** [3] **19**, 29 (1925).
- (71) CROWELL AND BRADT: *J. Am. Chem. Soc.* **55**, 1500 (1933).
- (72) CROXALL, SOWA, AND NIEUWLAND: *J. Am. Chem. Soc.* **56**, 2054 (1934).
- (73) CSANY: *Ber.* **52**, 1788 (1919).
- (74) DASI AND SEMPRONJ: *Gazz. chim. ital.* **63**, 681 (1933).
- (75) DAVIDSON AND LOWY: *J. Am. Chem. Soc.* **51**, 2978 (1929).
- (76) DARZENS: *Compt. rend.* **150**, 707 (1910).
- (77) DARZENS: *Compt. rend.* **189**, 766 (1929).
- (78) DARZENS: *Compt. rend.* **150**, 717 (1910).
- (79) DEHN: *J. Am. Chem. Soc.* **51**, 1167 (1929).
- (80) DELAVILLE: *Compt. rend.* **184**, 463 (1927).
- (81) DEUSS: *Rec. trav. chim.* **28**, 136 (1909).
- (82) DEUSS: *Rec. trav. chim.* **27**, 145 (1908).

- (83) DILTHEY: J. prakt. Chem. [2] **101**, 195 (1920).  
(84) DOBNER: Ann. **217**, 223 (1883).  
(84a) DOEBNER AND STACKMAN: Ber. **9**, 1918 (1876).  
(85) DOUGHERTY: J. Am. Chem. Soc. **51**, 576 (1929).  
(86) DRAKE AND BRONITSKY: J. Am. Chem. Soc. **52**, 3718 (1930).  
(87) DRECHSLER: Monatsh. **35**, 533 (1914).  
(88) DUBROV, LAVROSKII, GOLDSTEIN, FISH, AND MIKHNOVSKAYA: *Khimiya i Khoz'yaistvo* **22**, 19 (1932); C.A. **26**, 2853 (1932).  
(89) DUMREICHER: Ber. **15**, 1866 (1882).  
(90) DUPONT DE NEMOURS AND Co: British patent 397,852, Aug. 29, 1933; C.A. **28**, 1047 (1934).  
(91) DUVAL: Compt. rend. **146**, 341 (1908).  
(92) DUVAL: Bull. soc. chim. [4] **7**, 789 (1910).  
(93) EARL AND WILSON: J. Proc. Roy. Soc. N. S. Wales **65**, 178 (1932).  
(94) EATON, BLACK, AND FUSON: J. Am. Chem. Soc. **56**, 687 (1934).  
(95) EGLOFF AND MORRELL: U. S. patent 1,705,180 (1929); C.A. **23**, 2029 (1929).  
(96) EGLOFF AND MOORE: Chem. Met. Eng. **15**, 67 (1916).  
(97) EGLOFF AND LOWRY: J. Inst. Petroleum Tech. **14**, 562 (1928).  
(98) EGLOFF AND LOWRY: J. Inst. Petroleum Tech. **18**, 282 (1932).  
(99) EIJKMAN: Chem. Weekblad **2**, 229 (1905).  
(100) EIJKMAN: Chem. Weekblad **1**, 421 (1904).  
(101) EIJKMAN: Chem. Weekblad **4**, 727 (1907).  
(102) EIJKMAN: Chem. Weekblad **5**, 655 (1908).  
(103) ELBS: J. prakt. Chem. **41**, 145 (1890).  
(104) ENGLER AND ROUTALA: Ber. **42**, 4613 (1914).  
(105) EVISON AND KIPPING: J. Chem. Soc. **1931**, 2774.  
(106) FAEHLER: Ber. **46**, 1700 (1918).  
(107) FARAGHER AND GARNER: J. Am. Chem. Soc. **43**, 1715 (1921).  
(108) FAWORSKY: Ann. **354**, 325 (1907).  
(109) FISCHER AND SCHNEIDER: Ges. Abhandl. Kenntnis Kohle **1917**, I, 227; C.A. **13**, 3183 (1919).  
(110) FISCHER: Ber. **49**, 252 (1916).  
(111) FISCHER AND SHUBERT: Z. physiol. Chem. **155**, 99 (1926).  
(112) FISCHER AND TRIEBBS: Ber. **60**, 377 (1927).  
(112a) FOLDI: Ber. **61**, 1609 (1928).  
(113) FRANKE AND KLEIN: Monatsh. **33**, 1233 (1912).  
(113a) FLOOD AND NIEUWLANDS: J. Am. Chem. Soc. **50**, 2566 (1928).  
(114) FRANKFORTER AND KRITCHEVSKY: J. Am. Chem. Soc. **37**, 385 (1915).  
(115) FRANKFORTER AND KOKANTUR: J. Am. Chem. Soc. **37**, 2399 (1915).  
(116) FRANKFORTER AND KRITCHEVSKY: J. Am. Chem. Soc. **36**, 1529 (1914).  
(117) FRANKFORTER AND KRITCHEVSKY: J. Am. Chem. Soc. **36**, 1511 (1914).  
(118) FREUND: Monatsh. **17**, 395 (1896).  
(119) FRIEDEL AND CRAFTS: Compt. rend. **84**, 1392 (1877).  
(120) FRIEDEL AND CRAFTS: Ann. chim. phys. [6] **1**, 449 (1884).  
(121) FRIEDEL AND CRAFTS: Compt. rend. **84**, 1450 (1877).  
(122) FRIEDEL AND CRAFTS: Compt. rend. **85**, 74 (1877).  
(123) FRIEDEL AND CRAFTS: Ann. chim. phys. [6] **1**, 528 (1884).  
(124) FRIEDEL AND CRAFTS: British patent 4,769 (1877).  
(124a) FRIEDEL, CRAFTS, AND ADOR: Ber. **10**, 1854 (1877).  
(125) FRIEDMANN AND GATERMANN: Ber. **25**, 3525 (1892).  
(126) FRIES AND FINCK: Ber. **41**, 4371 (1908).

- (127) FUNK, SCHORMULLER, AND HENSINGER: *Z. anorg. allgem. Chem.* **205**, 361 (1932).
- (128) FUSON, KOSACIK, AND EATON: *J. Am. Chem. Soc.* **55**, 3799 (1933).
- (129) GABRIEL AND COLEMAN: *Ber.* **33**, 446 (1900).
- (130) GALLAY AND WHITBY: *Can. J. Research* **2**, 31 (1930).
- (131) GANGLOFF AND HENDERSON: *J. Am. Chem. Soc.* **39**, 1420 (1917).
- (132) GANZMULLER: *J. prakt. Chem.* **138**, 311 (1933).
- (133) GATTERMANN: *Ber.* **31**, 1150 (1898).
- (134) GATTERMANN: *Ann.* **357**, 313 (1909).
- (135) GATTERMANN: *Ber.* **28**, 2869 (1895).
- (136) GATTERMANN, EHRRARDT, AND MAISCH: *Ber.* **23**, 1199 (1894).
- (137) GATTERMANN, FRITZ, AND BECK: *Ber.* **32**, 1122 (1899).
- (138) GATTERMANN AND KOBNER: *Ber.* **32**, 282 (1899).
- (139) GATTERMANN AND KOCH: *Ber.* **30**, 1622 (1897).
- (140) GATTERMANN AND SCHMIDT: *Ann.* **244**, 43 (1887).
- (141) GEIGER: *Helv. Chim. Acta* **10**, 530 (1927).
- (142) GERHARDT: *Riechstoff Ind.* **5**, 67 (1930); *C.A.* **24**, 4897 (1930).
- (143) GILMAN AND DICKEY: *Rec. trav. chim.* **52**, 389 (1933).
- (143a) GILMAN AND WRIGHT: *Chem. Rev.* **11**, 323 (1932).
- (144) GILMAN AND CALLOWAY: *J. Am. Chem. Soc.* **55**, 4197 (1933).
- (144a) GILMAN AND CALLOWAY: Unpublished observations.
- (145) GILMAN, CALLOWAY, AND SMITH: *J. Am. Chem. Soc.* **56**, 220 (1934).
- (145a) GILMAN AND BROWN: Unpublished observations.
- (145b) GILMAN, BURTNER, CALLOWAY, AND TURCK: *J. Am. Chem. Soc.* **57**, 907 (1935).
- (145c) GILMAN AND BURTNER: *J. Am. Chem. Soc.* **57**, 909 (1935).
- (146) GILMAN, McCORKLE, AND CALLOWAY: *J. Am. Chem. Soc.* **56**, 745 (1934).
- (146a) GILMAN, CALLOWAY, AND McCORKLE: Unpublished observations.
- (147) GILMAN, CALLOWAY, AND BURTNER: *J. Am. Chem. Soc.* **57**, 906 (1935).
- (147a) GILMAN AND TURCK: Unpublished observations.
- (148) GOLDFARB: *J. Russ. Phys. Chem. Soc.* **62**, 1073 (1930); *C.A.* **25**, 2719 (1931).
- (149) GOLDSCHMIDT: *Ber.* **15**, 1066, 1425 (1882).
- (150) GOMBERG AND BAILOR: *J. Am. Chem. Soc.* **51**, 2233 (1929).
- (151) GRAEBE: *Ann.* **340**, 249 (1905).
- (152) GRIGNARD AND STRATFORD: *Compt. rend.* **178**, 2149 (1924).
- (153) GROGGINS AND NEWTON: *Ind. Eng. Chem.* **21**, 367 (1929).
- (154) GROGGINS AND NAGEL: *Ind. Eng. Chem.* **25**, 1083 (1933).
- (155) GROGGINS: *Chem. Markets* **26**, 479 (1930).
- (156) GROGGINS, STIRTON, AND NEWTON: *Ind. Eng. Chem.* **21**, 367 (1929).
- (157) GROGGINS, NAGEL, AND STIRTON: *Ind. Eng. Chem.* **26**, 1317 (1934).
- (157a) GROGGINS: *Unit Processes in Organic Synthesis*, p. 575. The McGraw-Hill Book Co., Inc., New York (1935).
- (158) GROGGINS: *Ind. Eng. Chem.* **23**, 152 (1931).
- (159) GROGGINS AND NAGEL: *Ind. Eng. Chem.* **26**, 1313 (1934).
- (160) GROGGINS AND NEWTON: *Ind. Eng. Chem.* **22**, 157 (1930).
- (161) GROGGINS: *Ind. Eng. Chem.* **22**, 620 (1930).
- (161a) GROGGINS: Private communication.
- (162) GRUCAREVIC AND MERZ: *Ber.* **6**, 1240 (1873).
- (163) GUREWITSCH: *Ber.* **30**, 2421 (1899).
- (164) GUSTAVIN: *Compt. rend.* **140**, 940 (1905).
- (165) GUSTAVIN: *Compt. rend.* **136**, 1065 (1903).
- (166) GUSTAVSON: *J. prakt. Chem.* [2] **37**, 108 (1888).

- (167) GUSTAVSON: J. prakt. Chem. [2] **68**, 209 (1903).  
(167a) GUSTAVSON: Ber. **11**, 2151 (1878).  
(168) GUSTAVSON: Ber. **13**, 157 (1880).  
(169) GUSTAVSON: Compt. rend. **146**, 640 (1908).  
(170) GUYOT: Compt. rend. **144**, 1051 (1907).  
(171) GUYOT: Compt. rend. **144**, 1120 (1908).  
(172) HALLA: Monatsh. **32**, 637 (1911).  
(173) HALLER AND GUYOT: Compt. rend. **144**, 947 (1907).  
(174) HALSE: J. prakt. Chem. **89**, 451 (1914).  
(175) HELLER: Ber. **45**, 792 (1912).  
(176) HELLER AND SCHULKE: Ber. **41**, 3627 (1908).  
(177) HELLER: Ber. **46**, 1497 (1913).  
(178) HELLER: Ber. **45**, 665 (1912).  
(179) HENDERSON AND GANGLow: J. Am. Chem. Soc. **38**, 1382 (1916).  
(180) HILL AND GRAFT: J. Am. Chem. Soc. **37**, 1840 (1915).  
(181) HILL: J. Am. Chem. Soc. **54**, 4105 (1932).  
(182) HINKEL: British patent 397,124, Aug. 15, 1933; C.A. **28**, 778 (1934).  
(183) HINSHELWOOD: The Kinetics of Chemical Change in Gaseous Systems, p. 218. Clarendon Press, Oxford (1933).  
(184) HINSHELWOOD: *ibid.*, p. 230.  
(185) HINSHELWOOD: *ibid.*, p. 247.  
(186) HOESCH: Ber. **43**, 1122 (1915).  
(187) HOFMANN AND WULFF: British patent 307,802, March 13, 1928; C.A. **24**, 127 (1930).  
(188) HOFFMANN, FARLOW, AND FUSON: J. Am. Chem. Soc. **55**, 2000 (1933).  
(189) HOLMES AND BEEMAN: Ind. Eng. Chem. **26**, 172 (1934).  
(190) HOMER: J. Chem. Soc. **91**, 1103 (1904).  
(191) HOMER: Proc. Cambridge Phil. Soc. **16**, 65 (1911); C.A. **5**, 1399 (1911).  
(192) HOMER: J. Chem. Soc. **97**, 1141 (1910).  
(193) HOPF: Ber. **65**, 483 (1932).  
(194) HOPF: Ber. **64**, 2739 (1931).  
(194a) HOUBEN: Ber. **59**, 2878 (1926).  
(195) HOUSTON, SWARTOUT, AND WARDWELL: J. Am. Chem. Soc. **52**, 4484 (1930).  
(196) HOUSTON AND LEWIS: J. Am. Chem. Soc. **53**, 2379 (1931).  
(197) HOUSTON AND EWING: J. Am. Chem. Soc. **37**, 2394 (1915).  
(198) HUFFORD: J. Am. Chem. Soc. **49**, 1845 (1927).  
(199) HUNT AND TURNER: J. Chem. Soc. **127**, 2667 (1925).  
(200) HUNTER AND YOHE: J. Am. Chem. Soc. **55**, 1248 (1933).  
(201) HURD: J. Am. Chem. Soc. **47**, 2777 (1925).  
(202) HUSTON AND STRICKLER: J. Am. Chem. Soc. **55**, 4317 (1933).  
(203) HUSTON AND GOODEMOOT: J. Am. Chem. Soc. **56**, 2432 (1934).  
(204) I. G. Farbenind. A-G: British patent 260,604, October 28, 1925; C.A. **21**, 3370 (1927).  
(205) I. G. Farbenind. A-G: French patent 669,739, February 16, 1929; C.A. **24**, 1866 (1930).  
(206) IPATIEFF AND KOMAREWSKY: J. Am. Chem. Soc. **56**, 1926 (1934).  
(207) ISBEKOV AND PLOTNIKOV: Z. anorg. Chem. **71**, 328 (1911).  
(208) JEPHCOTT: J. Am. Chem. Soc. **50**, 1189 (1928).  
(209) JACOBSEN: Ber. **14**, 2624 (1881).  
(210) JACOBSEN: Ber. **19**, 1209 (1886).  
(211) JACOBSEN: Ber. **20**, 900 (1887).

- (211a) JOHNSON AND LANE: J. Am. Chem. Soc. **43**, 348 (1921).  
(212) JORG: Ber. **60**, 1466 (1927).  
(212a) KABLUKOV AND KHANOV: J. Russ. Phys. Chem. Soc. **41**, 1755 (1909); C.A. **5**, 1419 (1911).  
(212b) KAISER: Ann. **257**, 95 (1890).  
(213) KANANTASSIS: Compt. rend. **194**, 461 (1932).  
(214) KASHTANOV: J. Gen. Chem. U. S. S. R. **2**, 515 (1932); C.A. **27**, 975 (1933).  
(215) KAUFLEDER: Ann. **433**, 48 (1923).  
(216) KAUFMANN: German patent 555,403, July 24, 1930; C.A. **26**, 5101 (1932).  
(217) KAVELER AND MONROE: J. Am. Chem. Soc. **50**, 2421 (1928).  
(217a) KHARASCH AND FLENNER: J. Am. Chem. Soc. **54**, 674 (1932).  
(218) KING: J. Am. Chem. Soc. **49**, 562 (1927).  
(219) KIRPAL: Monatsh. **31**, 295 (1910).  
(219a) KIRPAL: Monatsh. **30**, 355 (1909).  
(219b) KIRPAL: Monatsh. **27**, 372 (1906).  
(220) KIZHNER: J. Russ. Phys. Chem. Soc. **43**, 1163 (1911); C.A. **6**, 597 (1912).  
(221) KIZHNER: J. Russ. Phys. Chem. Soc. **46**, 1411 (1914).  
(222) KLIEGL AND HUBER: Ber. **53**, 1646 (1920).  
(223) KLING AND FLORENTIN: Compt. rend. **184**, 828 (1927).  
(224) KOENIGS: Ber. **24**, 3889 (1891).  
(225) KOHLER, HERITAGE, AND BURNLEY: Am. Chem. J. **44**, 60 (1910).  
(225a) KOHLER: Am. Chem. J. **42**, 375 (1909).  
(226) KOHN AND MULLER: Monatsh. **30**, 407 (1909).  
(227) KOHN: Monatsh. **58**, 108 (1931).  
(228) KOHN AND BUM: Monatsh. **33**, 923 (1912).  
(229) KONDAKOW: Chem. Zentr. **1894**, I, 1017.  
(230) KORCYNSKI: Bull. soc. chim. [4] **29**, 283 (1921).  
(231) KRANZLEIN: Aluminumchlorid in der organischen Chemie. Verein Deutscher Chemiker E. V., Berlin (1932).  
(232) KRAPIVIN: Bull. Soc. Imp. Nat. Moscow **1908**, 1; Chem. Zentr. **1910**, I, 1335.  
(233) KRISHNAMURTI: J. Madras Univ. **1928**, 5; C.A. **23**, 2164 (1929).  
(234) KROLLFEIFFER: Ber. **56**, 2360 (1923).  
(235) KUNCKELL AND ULEX: J. prakt. Chem. **86**, 518 (1912).  
(236) LACOURT: Bull. soc. chim. Belg. **38**, 1 (1929).  
(237) LAVAUX AND LOMBARD: Bull. soc. chim. [4] **7**, 539 (1910).  
(238) LAVAUX: Compt. rend. **146**, 345 (1908).  
(239) LAWRENCE: J. Am. Chem. Soc. **43**, 2577 (1921).  
(240) LAWRENCE: J. Am. Chem. Soc. **42**, 1871 (1920).  
(241) LAWRENCE AND ODDY: J. Am. Chem. Soc. **44**, 329 (1922).  
(242) LECHER: Ber. **46**, 2664 (1913).  
(243) LEENDERTSE, TULLENERS, AND WATERMAN: Rec. trav. chim. **52**, 515 (1933).  
(244) LIEBERMANN AND ZSUFFA: Ber. **44**, 202 (1911).  
(245) LIEBERMANN AND ZSUFFA: Ber. **44**, 852 (1911).  
(246) LILIENFELD: British patent 149,317, May 12, 1920; C.A. **15**, 434 (1927).  
(247) LIPP, KUPPERS, AND HOLL: Ber. **60**, 1575 (1927).  
(248) LOCKETT: J. Chem. Soc. **1932**, 1501.  
(249) LOHFERT: Ber. **63**, 1939 (1930).  
(250) LYONS AND BRADT: Ber. **60**, 60 (1927).  
(251) MCAFEE: Ind. Eng. Chem. **7**, 737 (1915).  
(252) MCAFEE: Ind. Eng. Chem. **21**, 670 (1929).  
(253) MCAFEE: U. S. patent 1,144,304 (1915); C.A. **9**, 2309 (1915).



- (254) McMULLEN: J. Am. Chem. Soc. **43**, 1965 (1921).  
(255) McMULLEN: J. Am. Chem. Soc. **44**, 2055 (1922).  
(256) MATSUMURA: J. Am. Chem. Soc. **52**, 4432 (1930).  
(256a) MATSUMURA: J. Am. Chem. Soc. **57**, 124 (1935).  
(257) MAUTHNER: J. prakt. Chem. **119**, 311 (1928).  
(258) MAYER AND SCHIFFNER: Ber. **67**, 67 (1934).  
(259) MAYER AND STAMM: Ber. **56**, 1424 (1923).  
(260) MEISSEL: Ber. **32**, 2419 (1899).  
(261) MEISENHEIMER AND CASPER: Ber. **54**, 1655 (1921).  
(262) MELNIKOV: J. Russ. Phys. Chem. Soc. **62**, 2019 (1930); C.A. **25**, 4228 (1931).  
(263) MENSCHUTKIN: Ann. inst. anal. phys. chim. Leningrad **2**, 61 (1922).  
(264) MENSCHUTKIN: J. Russ. Phys. Chem. Soc. **45**, 1710 (1913); C.A. **8**, 910 (1914).  
(265) MENSCHUTKIN: J. Russ. Phys. Chem. Soc. **42**, 1310 (1910); C.A. **6**, 734 (1912).  
(266) MENSCHUTKIN: J. Russ. Phys. Chem. Soc. **42**, 58 (1910); C.A. **5**, 1420 (1911).  
(267) MENSCHUTKIN: Iswiestja Petersburger Polytech. **13**, 1 (1910); C.A. **5**, 1434 (1911).  
(268) MENSCHUTKIN: *ibid.* **13**, 17 (1910); C.A. **5**, 1434 (1911).  
(269) MENSCHUTKIN: J. Russ. Phys. Chem. Soc. **41**, 1053, 1089 (1909); C.A. **3**, 1487 (1909).  
(270) MEYER: Ber. **29**, 846 (1896).  
(271) MICHAEL AND LEUPOLD: Ann. **379**, 263 (1911).  
(272) MICHAELIS AND ROJOHN: Ber. **50**, 737 (1917).  
(273) MICHAILENKO AND PROTASOWA: J. Russ. Phys. Chem. Soc. **58**, 347 (1926).  
(274) MICHLER: Ber. **9**, 400 (1876).  
(274a) MICHLER: Ber. **9**, 716 (1876).  
(275) MILLIGAN AND REID: J. Am. Chem. Soc. **44**, 206 (1922).  
(276) MINNIS: Organic Syntheses, Vol. 12, p. 62. Wiley and Sons, Inc., New York (1932).  
(277) MITTER AND RAY: J. Indian Chem. Soc. **9**, 247 (1932).  
(277a) MOELWYN-HUGHES: Kinetics of Reactions in Solution, Chap. III, p. 51. The Clarendon Press, Oxford (1934).  
(277b) MOELWYN-HUGHES: *ibid.*, Chap. VIII, p. 223.  
(278) MONTAGNE: Rec. trav. chim. **40**, 247 (1921).  
(279) MOCRE AND EGLOFF: Chem. Met. Eng. **17**, 61 (1917).  
(280) MORGAN AND PRATT: British patent 353,464 (1930); C.A. **26**, 5308 (1933).  
(281) MOSETTIG AND BURGER: J. Am. Chem. Soc. **52**, 2988 (1930).  
(282) MULLEN: J. Am. Chem. Soc. **43**, 1965 (1921).  
(283) MULLER, BAUER, WERCHITZ, AND WITTMAN: Z. Elektrochem. **38**, 227 (1932).  
(284) MULLER AND APPENZELLER: U. S. patent 1,699,671 (1929); C.A. **23**, 1141 (1929).  
(285) NASH AND MASON: Ind. Eng. Chem. **26**, 45 (1934).  
(286) NASH, STANLEY, AND BOWEN: J. Inst. Petroleum Tech. **16**, 830 (1930).  
(287) NASTYUKOV AND GURIN: J. Russ. Phys. Chem. Soc. **47**, 46 (1915); C.A. **9**, 1471 (1915).  
(288) NATELSON: J. Am. Chem. Soc. **56**, 1583 (1934).  
(289) NAUGATUCK CHEMICAL Co.: British patent 259,507, June 7, 1926; C.A. **21**, 3370 (1927).  
(290) NEMINSKI AND PLOTNIKOV: J. Russ. Phys. Chem. Soc. **40**, 391 (1908); C.A. **3**, 1147 (1909).  
(291) NENCKI: Ber. **32**, 2414 (1899).  
(291a) NENCKI: Ber. **30**, 1766 (1897).  
(291b) NENCKI: J. prakt. Chem. **25**, 273 (1882).

- (292) NENITZESCU, ISACESCU, AND IONESCU: *Ann.* **491**, 210 (1931).  
(293) NENITZESCU AND CANTUNIARI: *Ber.* **65**, 807 (1932).  
(294) NENITZESCU AND CANTUNIARI: *Ber.* **66**, 1097 (1933).  
(295) NENITZESCU AND CANTUNIARI: *Ber.* **65**, 1449 (1932).  
(296) NENITZESCU AND IONESCU: *Ann.* **491**, 189 (1931).  
(297) NENITZESCU AND CICOS: *Ber.* **66**, 969 (1933).  
(298) NENITZESCU AND ISACESCU: *Ber.* **66**, 1100 (1933).  
(299) NIEDERL AND RILEY: *J. Am. Chem. Soc.* **56**, 2412 (1934).  
(300) NIGGEMAN: *Ges. Abhandl. Kenntnis Kohle* **1917**, **1**, 255; *C.A.* **13**, 3184 (1919).  
(301) NICOLET AND DEMILT: *J. Am. Chem. Soc.* **49**, 1103 (1927).  
(302) NOLLER AND ADAMS: *J. Am. Chem. Soc.* **46**, 1889 (1924).  
(303) NORRIS AND YOUNG: *J. Am. Chem. Soc.* **46**, 2580 (1924).  
(304) NORRIS: *Ind. Eng. Chem.* **16**, 184 (1924).  
(305) NORRIS AND COUCH: *J. Am. Chem. Soc.* **42**, 2329 (1920).  
(306) OLIVIER: *Rec. trav. chim.* **37**, 205 (1908).  
(307) OLIVIER: *Rec. trav. chim.* **33**, 244 (1913).  
(308) OLIVIER: *Rec. trav. chim.* **33**, 91 (1913).  
(309) OLIVIER: *Chem. Weekblad* **11**, 372 (1914).  
(310) OLIVIER: *Rec. trav. chim.* **35**, 166 (1915).  
(311) OLIVIER: *Rec. trav. chim.* **35**, 109 (1915).  
(312) OLIVIER: *Rec. trav. chim.* **37**, 241 (1918).  
(313) OLIVIER: *Rec. trav. chim.* **45**, 817 (1926).  
(314) OLIVIER AND BERGER: *Rec. trav. chim.* **45**, 710 (1926).  
(315) OLIVIER AND BERGER: *Rec. trav. chim.* **46**, 605 (1927).  
(316) OLIVIER AND BOESEKEN: *Verslag Akad. Wetenschappen* **21**, 979 (1913); *C.A.* **8**, 1424 (1914).  
(317) OLSON: *U. S. patent* 1,935,914, Nov. 21, 1933; *C.A.* **28**, 778 (1934).  
(318) PACE: *Gazz. chim. ital.* **59**, 578 (1929).  
(319) PACKENDORF, ZENLINSKII, AND LEDER-PACKENDORFF: *Ber.* **66**, 1069 (1933).  
(320) PECHMANN: *Ber.* **12**, 2126 (1879).  
(321) PERRIER: *Ber.* **33**, 53 (1900).  
(322) PERRIER: *Compt. rend.* **116**, 1298 (1893).  
(323) PERRIER AND CAILLE: *Compt. rend.* **146**, 769 (1908).  
(324) PFEIFFER ET AL: *Ann.* **376**, 285 (1910).  
(325) PFEIFFER, KOLLBACH, AND HAACK: *Ann.* **460**, 138 (1928).  
(326) PFEIFFER AND HAACK: *Ann.* **460**, 156 (1928).  
(327) PFEIFFER AND OCHAI: *J. prakt. Chem.* **136**, 125 (1933).  
(328) PHELIPI: *Monatsh.* **32**, 631 (1911).  
(329) PHILLIPS: *Chem. Met. Eng.* **17**, 61, 128 (1917).  
(330) PICCARD: *Ber.* **7**, 1785 (1874).  
(331) PICKLES AND WEITZMANN: *Proc. Chem. Soc. London* **20**, 220 (1904).  
(332) PICTET AND LERCZYNSKA: *Bull. soc. chim.* [4] **19**, 326 (1916).  
(333) PLOEG: *Rec. trav. chim.* **45**, 342 (1926).  
(334) PLOTNIKOV: *J. Russ. Phys. Chem. Soc.* **45**, 1135 (1913); *C.A.* **8**, 304 (1914).  
(335) PLOTNIKOV AND BENDETSKY: *Z. physik. Chem.* **127**, 225 (1927).  
(336) PLOTNIKOV: *J. Russ. Phys. Chem. Soc.* **42**, 1589 (1910); *C.A.* **6**, 14 (1912).  
(337) PORTER: *Molecular Rearrangements*, p. 116. The Chemical Catalog Co., Inc., New York (1928).  
(338) PRINS: *J. prakt. Chem.* **89**, 425 (1914).  
(339) PRINS: *J. prakt. Chem.* **89**, 414 (1914).  
(340) PRINS: *Rec. trav. chim.* **51**, 1065 (1932).

- (341) PRINS: Chem. Weekblad **24**, 615 (1927).  
(342) PUMMERER AND BINAFL: Ber. **54**, 2768 (1921).  
(342a) PUMMERER AND BINAFL: Ber. **54**, 3095 (1921).  
(343) RABTSEVITCH-ZUBKOVSKII: J. Russ. Phys. Chem. Soc. **46**, 698 (1914); C.A. **9**, 1749 (1917).  
(344) RADZIEWANOWSKI: Ber. **27**, 3235 (1894).  
(345) RAY: J. Chem. Soc. **117**, 1335 (1920).  
(346) REICHSTEIN: Helv. Chim. Acta **13**, 349 (1930).  
(347) REICHSTEIN: Helv. Chim. Acta **13**, 356 (1930).  
(348) REICHSTEIN: Helv. Chim. Acta **13**, 345 (1930).  
(349) REICHSTEIN, ZSCHOKKE, AND GEORG: Helv. Chim. Acta **14**, 1277 (1931).  
(350) REILLY AND DRUMM: J. Chem. Soc. **1927**, 2814.  
(351) RICE: J. Am. Chem. Soc. **53**, 3153 (1931).  
(352) RIDDELL AND NOLLER: J. Am. Chem. Soc. **52**, 4365 (1930).  
(353) RIDDELL AND NOLLER: J. Am. Chem. Soc. **54**, 290 (1932).  
(354) RIVIER AND KUNZ: Helv. Chim. Acta **15**, 376 (1932).  
(355) ROSENMUND AND SCHULZ: Arch. Pharm. **265**, 308 (1927).  
(356) ROSENMUND AND SCHNURR: Ann. **460**, 56 (1928).  
(357a) ROSENMUND AND LOHFERT: Ber. **61**, 2601 (1928).  
(357b) ROZYCKI: Ber. **30**, 2428 (1899).  
(358) RUZICKA, PIETH, REICHSTEIN, AND EHMANN: Helv. Chim. Acta **16**, 275 (1933).  
(359) RUBIDGE AND QUA: J. Am. Chem. Soc. **36**, 732 (1914).  
(360) RUFF: Ber. **34**, 1749 (1901).  
(361) RUFF: Ber. **35**, 4453 (1902).  
(362) SABETAY: Compt. rend. **192**, 1109 (1931).  
(363) SCHAARSCHMIDT: Z. angew. Chem. **37**, 286 (1924).  
(364) SCHAARSCHMIDT, BALZERKIEWICS, AND GANTE: Ber. **58**, 499 (1925).  
(365) SCHAARSCHMIDT, HERMANN, AND SZEMZO: Ber. **58**, 1914 (1925).  
(366) SCHAARSCHMIDT AND IRENEU: Ber. **48**, 1826 (1915).  
(367) SCHAARSCHMIDT: Ber. **57**, 2065 (1924).  
(368) SCHEIBLER: Ber. **48**, 1815 (1915).  
(369) SCHERING-KAHLBAUM A.-G.: British patent 397,505, Aug. 21, 1933; C.A. **28**, 1048 (1934).  
(370) SCHIFF: Ber. **10**, 1501 (1877).  
(371) SCHLEICHER AND BUTTGENBACH: J. prakt. Chem. **105**, 355 (1923).  
(372) SCHLENK AND BERGMAN: Ann. **464**, 32 (1928).  
(373) SCHMIDLIN AND LANG: Ber. **45**, 899 (1912).  
(374) SCHMIDT: J. Am. Chem. Soc. **53**, 1172 (1930).  
(375) SCHMIDT: Organo-metalverbindungen, p. 213. Wissenschaftliche Verlagsgesellschaft, Stuttgart (1934).  
(376) SCHOLL: Ber. **36**, 10 (1903).  
(377) SCHOLL, SEER, AND WELTZENBACH: Ber. **43**, 2203 (1910).  
(378) SCHOLL AND NEOVIUS: Ber. **44**, 1075 (1911).  
(379) SCHOLL AND SEER: Monatsh. **33**, 1 (1912).  
(380) SCHOLL AND SEER: Ann. **394**, 111 (1912).  
(381) SCHOLL AND SEER: Ber. **55**, 109 (1922).  
(382) SCHOLL AND SWARZER: Ber. **55**, 324 (1922).  
(383) SCHOLL AND SEER: Ber. **55**, 330 (1922).  
(384) SCHOLL ET AL.: Ann. **494**, 201 (1932).  
(385) SCHORGER: J. Am. Chem. Soc. **39**, 2671 (1917).  
(386) SCHRAUTH: Ber. **57**, 854 (1924).

- (387) SCHROETER: Ber. **57**, 1990 (1924).  
(388) SCHROETER: Ber. **57**, 1997 (1924).  
(389) SCHROETER: Ber. **60**, 2037 (1927).  
(390) SCHWENK AND WALDENMANN: Z. angew. Chem. **45**, 17 (1932).  
(391) SEER: Monatsh. **32**, 143 (1911).  
(392) SHEPARD: Canadian patent 265,521, Nov. 21, 1926; C.A. **21**, 917 (1927).  
(392a) SHOESMITH AND MCGEHEEN: J. Chem. Soc. **1930**, 2231.  
(393) SILVER AND LOWY: J. Am. Chem. Soc. **56**, 2428 (1934).  
(394) SIEMANS AND HALSKE AKT.-GES.: German patent 289,909 (1914); C.A. **10**, 2622 (1916).  
(395) SIDGWICK: Electronic Theory of Valency, p. 175. The Clarendon Press, Oxford (1927).  
(396) SIDGWICK: *ibid.*, p. 266.  
(397) SIMONIS AND LEAR: Ber. **59**, 2908 (1926).  
(398) SIMONIS AND DANISHEVSKI: Ber. **59**, 2914 (1926).  
(400) SMITH: J. Am. Chem. Soc. **55**, 849 (1933).  
(401) SMITH: J. Am. Chem. Soc. **55**, 3718 (1933).  
(402) SMITH: J. Am. Chem. Soc. **56**, 717 (1934).  
(403) SMITH: J. Am. Chem. Soc. **46**, 1920 (1921).  
(404) SMYTHE: J. Chem. Soc. **121**, 1270 (1922).  
(405) SOWA, HINTON, AND NIEUWLAND: J. Am. Chem. Soc. **54**, 3694 (1932).  
(406) STADNIKOFF AND BARYSCHEWA: Ber. **61**, 1996 (1928).  
(407) STADNIKOFF AND GOLDFARB: Ber. **61**, 2341 (1928).  
(408) STADNIKOFF AND KASCHTANOW: Ber. **61**, 1389 (1928).  
(409) STANLEY: J. Soc. Chem. Ind. **49**, 349 (1930).  
(410) STAUDINGER: Ber. **45**, 1594 (1912).  
(411) STAUDINGER, SCHLENKER, AND GOLDSTEIN: Helv. Chim. Acta **4**, 334 (1921).  
(412) STAUDINGER, GOLDSTEIN, AND SCHLENKER: Helv. Chim. Acta **4**, 342 (1921).  
(413) STAUDINGER: Ber. **41**, 3558 (1908).  
(414) STAUDINGER: Ber. **41**, 3566 (1908).  
(415) STEEL: J. Chem. Soc. **83**, 1470 (1903).  
(416) STEINKOPF: Ann. **413**, 343 (1917).  
(417) STEINKOPF: Ann. **430**, 98 (1923).  
(418) STEINKOPF AND FREUND: Ber. **47**, 411 (1914).  
(419) STEINKOPF AND SCHUBART: Ann. **424**, 1 (1921).  
(420) STEPHENS: J. Am. Chem. Soc. **43**, 1950 (1921).  
(421) STEVENS: J. Am. Chem. Soc. **56**, 450 (1934).  
(422) STOCKHAUSEN AND GATTERMAN: Ber. **25**, 3521 (1892).  
(423) SZAYNA: Przemyśl Chem. **12**, 637 (1928).  
(424) THOMAS: Compt. rend. **125**, 1211 (1898).  
(425) THOMAS, BOWDEN, AND JONES: J. Chem. Soc. **1930**, 473.  
(426) THOMAS AND CARMODY: J. Am. Chem. Soc. **54**, 2480 (1932).  
(427) THOMAS AND CARMODY: Ind. Eng. Chem. **24**, 1125 (1932).  
(428) TICHY: Paliva a Topeni **11**, 85, 100 (1929); C.A. **24**, 4925 (1930).  
(428a) TILITSCHIEJEW AND KURYNDIN: Neftyanoe Khozjalstvo **19**, 586 (1930); C.A. **25**, 3469 (1931).  
(429) ULICH: Z. physik. Chem., Bodenstein Festband, p. 423 (1931).  
(430) UNGER: Ann. **504**, 267 (1933).  
(431) UNGER: Ber. **65**, 467 (1932).  
(432) VALIK AND VALIK: British patent 398,136, Sept. 7, 1933; C.A. **28**, 1047 (1934).  
(433) VAN DUIN: Rec. trav. chim. **46**, 256 (1927).

- (433a) VARET AND VIEUNE: Bull. soc. chim. [2] **47**, 418 (1887).
- (434) VENKATARAMAN AND BHARADWAJ: Current Sci. **2**, 50 (1934).
- (435) VERLEY: Bull. soc. chim. [3] **17**, 909 (1897).
- (436) VORLANDER AND FRITZCHE: Ber. **46**, 1793 (1913).
- (437) VORLANDER AND FRIEDBERG: Ber. **56**, 1144 (1923).
- (438) WALKER: J. Chem. Soc. **85**, 1091 (1904).
- (439) WARD: J. Chem. Soc. **119**, 850 (1921).
- (440) WATERMANN: Chimie & industrie, Special No., 469, 505, June, 1933.
- (441) WEINSTOCK AND FUSON: J. Am. Chem. Soc. **56**, 1241 (1934).
- (442) WERTYPOROCH AND ALTMAN: Z. physik. Chem. **168**, 1 (1933).
- (443) WERTYPOROCH AND SAGEL: Ber. **66**, 1306 (1933).
- (444) WERTYPOROCH, KOWALSKI, AND ROESKE: Ber. **66**, 1232 (1933).
- (445) WERTYPOROCH AND FARNIK: Ann. **491**, 265 (1931).
- (446) WERTYPOROCH AND FIRLA: Ann. **500**, 287 (1933).
- (447) WIBAUT, KIEKMAN, AND RUTGERS: Rec. trav. chim. **47**, 477 (1928).
- (448) WIELAND AND HASEGAWA: Ber. **64**, 2516 (1931).
- (449) WIELAND AND BETTAG: Ber. **55**, 2246 (1922).
- (450) WIELAND AND DORRER: Ber. **58**, 818 (1925).
- (451) WILLEGERODT AND SCHOLTZ: J. prakt. Chem. [2] **81**, 394 (1910).
- (452) WILLEGERODT AND KLINGER: J. prakt. Chem. **85**, 189 (1912).
- (453) WILSON AND FULLER: Ind. Eng. Chem. **14**, 406 (1922).
- (454) WINTER AND FREE: Brennstoff-Chem. **12**, 451 (1931).
- (455) WOHL AND WERTYPOROCH: Ber. **64**, 1357 (1931).
- (456) WOLFE: Ber. **14**, 2031 (1881).
- (457) WOLFFENSTEIN AND HARTWICH: Ber. **48**, 2043 (1915).
- (458) WOJAHN: Arch. Pharm. **271**, 417 (1933).
- (459) WOODWARD, BORCHERDT, AND FUSON: J. Am. Chem. Soc. **56**, 2103 (1934).
- (460) ZEAVIN AND FISCHER: J. Am. Chem. Soc. **54**, 3738 (1932).
- (461) ZELINSKII AND TUROVA-POLLAK: Ber. **65**, 1171 (1932).
- (462) ZELINSKII AND TARASSOVA: Ber. **65**, 1249 (1932).
- (463) ZELINSKII AND TUROVA-POLLAK: Ber. **62**, 1658 (1928).
- (464) ZELINSKII AND LAVROVSKI: Ber. **61**, 1054 (1928).
- (465) ZELINSKII AND SMIRNOV: Brennstoff-Chem. **6**, 249 (1925).
- (466) ZINCKE AND SUHL: Ber. **39**, 4148 (1907).
- (467) ZINCKE: Ber. **2**, 737 (1869).
- (468) ZINCKE: Ann. **159**, 367 (1871).
- (469) ZINCKE: Ber. **4**, 298 (1871).
- (470) ZINCKE: Ber. **161**, 93 (1872).

# A SYMPOSIUM ON PHOTOCHEMISTRY<sup>1</sup>

## INTRODUCTION TO THE SYMPOSIUM

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In introducing this symposium, it is of interest to turn back to another symposium on photochemistry, held by the Faraday Society at Oxford just ten years ago (23). At that meeting the discussion was divided almost equally between what were then two of the greatest fields of interest in photochemistry: Einstein's law of photochemical equivalence, and the mechanism of photochemical reactions. The papers and discussion which comprise the present symposium, although not offered as a complete cross section of modern photochemical problems, give nevertheless a fair idea of the extent to which, in the intervening decade, the latter of these two fields of interest has absorbed the former.

Even prior to 1925 it was recognized that Einstein's derivation could be applied only to the original elementary process of absorption in a photochemical reaction, and shortly thereafter it was suggested by H. S. Taylor (6) that the relation between primary absorption and secondary reaction be generalized in the following manner,—“The absorption of light is a quantum process involving one quantum per absorbing molecule (or atom). The photochemical yield is determined by the thermal reactions of the system produced by the light absorption.”

This concept has proven highly fruitful in the interpretation of photochemical phenomena. As early as 1913 it moved Bodenstein (1) to introduce the idea of chain reactions into chemistry; it has been applied to almost every photochemical reaction which has been carefully studied since that time. The principles relating absorption spectra and the primary process, due in no small part to the fundamental contributions of Franck, have become, for the simpler molecules at least, well understood and generally accepted by photochemists during recent years. Thus the Faraday Society symposium of 1925 was marked by the presentation by

<sup>1</sup> Held under the auspices of the Division of Physical and Inorganic Chemistry at the Ninetieth Meeting of the American Chemical Society at San Francisco, California, August 20, 1935.

Franck of his ideas on the adiabatic dissociation of molecules by light, which have since become part of standard photochemical theory.

As a result of these developments, interest in quantum yields has become limited almost entirely to the extent to which they are useful in interpreting the secondary mechanism of photochemical reactions. It must not be assumed, however, that in every case one molecule becomes activated or dissociated for every quantum absorbed by the light sensitive species; that is to say, it must not be assumed that the primary quantum yield is always unity. In polyatomic molecules the primary yield may be reduced by an "inner filter" action due to the existence of two or more absorbing bonds in the molecule, absorption by only one of which can be effective in producing reaction (7, 13). In processes involving the primary photochemical dissociation of molecules (continuous or diffuse absorption spectra), an internal redistribution of absorbed energy may occur which prevents dissociation and so reduces the primary quantum yield (14). In solutions, as Franck and Rabinowitsch (8) have emphasized, the primary yield may be reduced by collisional deactivation during the period between absorption and dissociation. Although the extent to which these possibilities may be effective is as yet uncertain, they must be kept in mind whenever use is made of quantum yields in interpreting photochemical reaction mechanisms.

It is well known that in general the larger the number of atoms in a molecule the more difficult it becomes to effect a reliable correlation between the absorption spectrum and the primary process. In most cases ten or twelve atoms seem to be about the limit of molecular size for which vibrational structure in absorption can be observed. For example, even though the fluorescence of acetone vapor indicated the formation of activated molecules by absorption, several attempts were made before it could be proven that the absorption spectrum was other than continuous (16). Conjugated unsaturation extends the limit of molecular size for which distinct structure can be observed.

A comparison of the absorption spectra of several of the aldehydes is of interest in this respect. In figure 1 the band reproduced is the near ultra-violet absorption characteristic of the carbonyl bond. Although the structure becomes progressively weaker as the alkyl residue becomes larger, there is no photochemical evidence to indicate any marked difference in the primary process in the different aldehydes. It seems likely that the disappearance of structure in the higher aldehydes is due to an actual overlapping of the energy levels in the molecule rather than to a lack of sufficient dispersion in the spectrograph used. Contrasted with this behavior is the effect of introducing a conjugated double bond into the molecule. Figure 2 compares the absorption of crotonaldehyde

(eleven atoms) with that of propionaldehyde (ten atoms).<sup>2</sup> In crotonaldehyde the carbonyl absorption band is shifted several hundred Ångström units toward the red, and its vibrational fine structure is distinctly sharpened as compared with propionaldehyde.

Although the pioneer researches of the elder Warburg have never been excelled in regard to painstaking care and accuracy of manipulation, experimental methods in photochemistry have been standardized to the extent that quantum yields for a given reaction may be measured by several independent investigators with results agreeing to within 1 or 2 per cent (10, 11, 15, 26). Improvement in analytical methods, together with standardization of methods for obtaining monochromatic radiation and

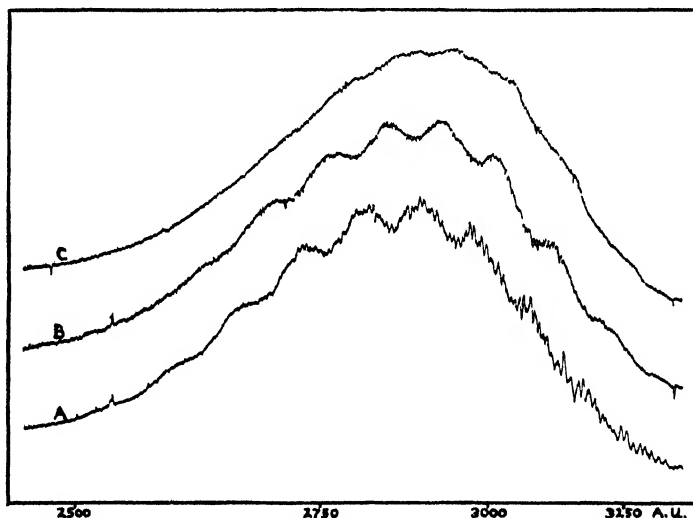


FIG. 1. Tracings of the near ultra-violet absorption spectra of (A) acetaldehyde, (B) propionaldehyde, (C) butyraldehyde.

measuring its intensity, have reached the point where one can confidently attach significance to small changes in reaction rates or products with changes in wave length, concentration, or temperature. Promising actinometric methods (10, 12, 26) are coming into wider use.

Contrasting sharply with the progress in our understanding of the primary process, and with the development of experimental technique, the determination of secondary reaction mechanisms still remains one of the greatest problems of photochemistry. In most cases photochemical sec-

<sup>2</sup> The author is indebted to Drs. F. E. Blacet and W. G. Young of the University of California at Los Angeles, and to Mr. Leo Levanas of Stanford University, for the use of the spectrograms from which these tracings were recorded.



ondary reactions, in gases at least, involve free atoms or radicals about which not enough is known. Even the detection of free atoms or radicals as intermediate products in photochemical reactions has been accomplished in only a few cases; measurement of their stationary concentration has been done scarcely at all. Methods are developing which give promise of making this possible. The para-ortho hydrogen conversion has been applied by Geib and Harteck (9) to estimate the stationary concentration of hydrogen atoms in the photosynthesis of hydrogen chloride, and by Farkas and Harteck (5) to estimate the atomic hydrogen concentration during the photolysis of ammonia. Corrections must be made for the amount of normal hydrogen produced by the reaction itself (4), and in

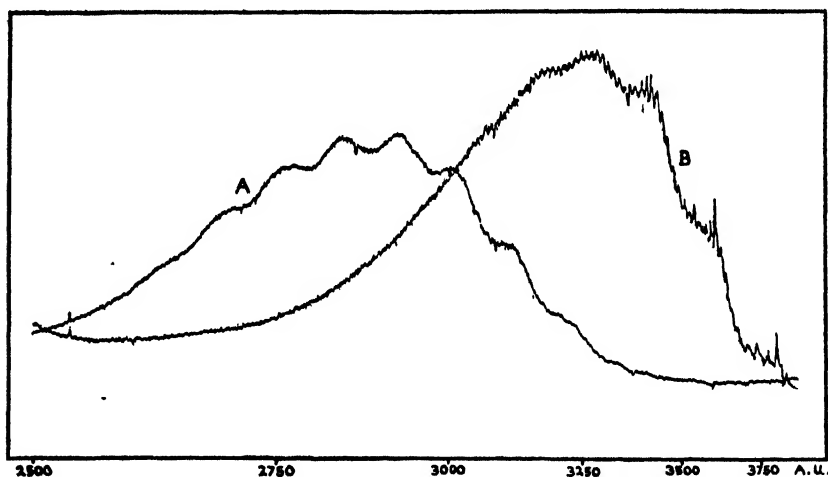


FIG. 2. Tracings of the near ultra-violet absorption spectra of (A) propionaldehyde and (B) crotonaldehyde.

general the method must be used with caution as paramagnetic molecules or radicals, such as  $O_2$ ,  $CH_3$ , or halogen atoms, will also produce the conversion (3). In fact, this conversion has been applied by Patat and Sachsse (19) to estimate the stationary concentration of methyl radicals (or hydrogen atoms) during the thermal decomposition of acetaldehyde, and by West (25) as an indicator of the formation of methyl radicals and iodine atoms when methyl iodide and acetone are exposed to light.

Emission spectra give evidence of the primary formation of free atoms or radicals whenever the absorbed light has sufficient energy to produce dissociation into electronically excited particles which lose their excitation by emission. Terenin, for example, has recently reported (24) the emission of bands belonging to OH, CN, and  $NH_2$  radicals when such mole-

cules as  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{OH}$ ,  $\text{HCOOH}$ ,  $\text{CH}_3\text{CN}$ , and  $\text{NH}_3$  are exposed to radiation of 1400–1600 Å.U.

Since most free radicals possess absorption spectra in the visible or near ultra-violet, observations via absorption would appear to offer one of the most direct methods for observing those radicals during the course of a reaction. Bonhoeffer and Reichardt (2) were able to observe the absorption of OH radicals in thermally dissociated water vapor, and Oldenberg (17) used absorption under high dispersion to detect and estimate the life period of non-excited hydroxyl radicals produced by the electric discharge through water vapor. Oldenberg emphasizes the necessity of high resolving power in the spectrograph used to photograph the absorption, but whether this method can be made sufficiently sensitive to observe free radicals at the concentrations in which they are produced in photochemical reactions remains to be determined.

The removal of metallic films by alkyl radicals after the method of Paneth (18, 21) presents another possibility, although more limited in scope. Difficulties arise in the application of this method to the study of free radicals produced during photochemical reactions, since the gases under observation must be streamed past the light source at low pressures in a tube of small dimensions, with the result that the amount of absorption and hence the amount of reaction are very small. Despite these difficulties, Pearson (20) reports the rapid removal of visible mirrors of antimony, tellurium, and lead by means of the radicals produced when acetone and other ketones are exposed to light. He estimates the half-life of the active agents from acetone as  $5.3 \times 10^{-8}$  sec., which is in close agreement with the half-life of  $5.8 \times 10^{-8}$  sec. found by Paneth and Hofeditz for free methyl.

R. A. Mortensen and the author, exposing lead tetramethyl vapor under similar conditions to the 2537 Å.U. line of a high-intensity mercury arc were able to decompose only about  $10^{13}$  molecules per second. Even assuming that all methyl groups from the decomposed molecules were able to survive as free radicals and react with a lead mirror further down the tube, the amount of lead so removed would amount to only 0.01 mg. per hour. By using a radioactive isotope of lead (radium D) to form the mirror and following the transfer of radioactivity from the mirror to the trap, we were able to increase the sensitivity of the method so that the formation of free radicals in the above reaction was easily followed. It is possible by observing the removal of deposits of radioactive metals to observe stationary concentrations of methyl radicals corresponding to a partial pressure of as low as  $10^{-8}$  mm.

Even if the active particles, free radicals or atoms, which may be produced during a photochemical reaction, together with their stationary

concentrations, are known, one is still faced with the problem of determining what reactions can occur and to what extent each possible reaction does occur. Photochemistry and chemical kinetics meet on common ground in that secondary reactions are thermal reactions and so have specific rate constants and characteristic energies of activation. As Bates points out, one of the greatest contributions that could be made to photochemistry at the present time would be a reliable codification of these constants for a number of individual reactions.

The difficulties in the way of determining these constants are discussed by Bates. The direct study of individual processes, as, for example, the study of the reaction between chlorine atoms and hydrogen molecules by Rodebush and Klingelhofer (22), or the reaction between oxygen atoms and nitric oxide reported by Rodebush, is one of the most satisfying ways of obtaining the desired information. Unfortunately, the results of different investigators on the same individual reaction, as, for example, the studies of the recombination of hydrogen atoms discussed by Bates, are in wide disagreement. Moreover, it is uncertain as to whether the constants determined for a given reaction occurring alone can be applied to that same reaction occurring in the presence of other molecules.

In photochemistry, as in reaction kinetics, the theoretical treatment of reactions in solution has progressed less rapidly than the treatment of reactions in gases. As Dickinson shows, direct comparison of reactions in the gas phase and in solution, at least in inert solvents, provides one of the most valuable methods of approach to the latter. Photochemistry, through the information given by absorption spectra and quantum yields, perhaps has the advantage over thermal reaction kinetics in comparisons of this sort.

When dealing with reactions in active or ionizing solvents, where ions, ionic complexes, or solvated molecules may be involved, comparisons between gas and solution become strictly limited. The application of kinetic rate laws, as discussed by Rollefson, appears to offer one of the most powerful tools for unraveling the mechanism of reactions in non-ideal solutions.

Of all reactions which may be classed as photochemical, none has been more subtle in resisting solution by investigation than has the carbohydrate photosynthesis in green plants. Nor has any other photochemical reaction more far-flung significance than photosynthesis. Franck has suggested a mechanism, based on recognized photochemical principles, which will explain the unique energetic relations as well as other characteristics of the photosynthetic process, and which is certain to stimulate further thought and experiment on this important problem.

## REFERENCES

- (1) BODENSTEIN: Z. physik. Chem. **85**, 329 (1913).
- (2) BONHÖFFER AND REICHARDT: Z. physik. Chem. **139**, 75 (1928).
- (3) FARKAS, A.: Ortho Hydrogen, Para Hydrogen, and Heavy Hydrogen, p. 79. Cambridge University Press, Cambridge (1935).
- (4) FARKAS, A.: *ibid.* p. 104.
- (5) FARKAS AND HARTECK: Z. physik. Chem **25B**, 257 (1934).
- (6) First Report of the Committee on Photochemistry, National Research Council, Circular 81 (1928). J. Phys. Chem. **32**, 527 (1928).
- (7) FORBES AND HEIDT: J. Am. Chem. Soc. **55**, 2407, 2701 (1933).
- (8) FRANCK AND RABINOWITSCH: Trans. Faraday Soc **30**, 120 (1934).
- (9) GEIB AND HARTECK: Z. physik. Chem. **15B**, 116 (1931).
- (10) HARRIS AND KAMINSKY: J. Am. Chem. Soc **57**, 1154 (1935)
- (11) HOLMES AND DANIELS: J. Am. Chem. Soc **56**, 630 (1934).
- (12) LEIGHTON, W. G , AND FORBES, G, S : J. Am. Chem Soc. **52**, 3139 (1930).
- (13) LEIGHTON, P. A., AND LUCY, A.: J. Chem. Physics **2**, 759 (1934).
- (14) NORRISH, CRONE, AND SALTMARSH: J Chem Soc **1934**, 1463.
- (15) NORTON: J. Am. Chem Soc. **56**, 2295 (1934).
- (16) NOYES, DUNCAN, AND MANNING: J. Chem Physics **2**, 717 (1934).
- (17) OLDENBERG: J. Chem. Physics **3**, 266 (1935).
- (18) PANETH AND HOFEDITZ: Ber. **62**, 1335 (1929).
- (19) PATAT AND SACHSSE: Naturwissenschaften **15**, 247 (1935).
- (20) PEARSON: J. Chem. Soc. **1934**, 1718; **1935**, 1151.
- (21) RICE, F. O.: Trans. Faraday Soc. **30**, 166 (1934).
- (22) RODEBUSH AND KLINGELHOFER: J. Am Chem Soc. **55**, 130 (1933).
- (23) Symposium on Photochemistry: see Trans. Faraday Soc. **21**, 438 (1925).
- (24) TEREININ: J. Chem. Physics **3**, 436 (1935).
- (25) WEST: J. Am. Chem. Soc. **57**, 1931 (1935).
- (26) WEYDE AND FRANKENBERGER: Trans. Faraday Soc **28**, 561 (1931).



# RATE CONSTANTS OF REACTIONS OF ATOMS AND RADICALS AS DERIVED FROM DIFFERENT SOURCES

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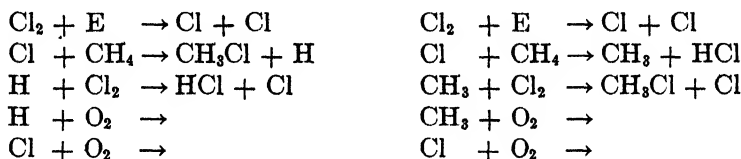
Almost all photochemical reactions are of the type which have come to be called complex. For example, at present we know of no reaction which may be described as a bimolecular process in which the activated reactant is produced by absorption of radiation rather than by thermal excitation. We may go further and make the statement that, with not more than one or two exceptions, all of the photoreactions which have been studied take place through the intermediate formation of atoms and radicals. Once formed, these react just as though we could produce them in a stable condition and introduce them into a reaction vessel. Since these processes are thus thermal in nature, it is not surprising to find the same ones occurring not only in different photoreactions but also in various thermal reactions. Those radical reactions which are common to several different over-all reactions of course take on added interest and importance.

The individual steps which consist of reactions of atoms and radicals may of course be classed as uni-, bi-, or tri-molecular, and each have their appropriate specific reaction constants. The value of these (either absolute or relative) may often be obtained from a kinetic study of a complex reaction in which they are involved. The difficulties in such a procedure are many. Often it is not known whether the steps postulated in the mechanism actually occur or not. Too frequently it is possible to write down two (or more) entirely different series of steps, both (or all) of which are in agreement with experiment. Direct determination of the transient existence of the radical intermediaries in reactions is at present practically impossible. Much has been said of the spectroscopic method in this connection, but this does not give us much more assurance than to prove the general fact that radicals may exist. To obtain emission spectra of these radicals a large amount of surplus energy is needed, which cannot usually be obtained under the conditions imposed. In fact this method may be misleading. For example, the presence of OH bands in the flame of burning hydrogen has led some to believe that this radical occurs in the photoreactions involving hydrogen and oxygen, which fact, because of other

evidence, I for one do not believe to be true. However, a recent paper of Oldenberg's has given a method of obtaining evidence of radicals through absorption spectra under high dispersion. This is a yet unexplored possibility which might in some cases yield the desired result.

But we should like to know definitely what radicals occur in a given process and what the specific rate constants of their various reactions are. Very often if we knew the values of the rate constants of even some of the possible reactions we should be able to write the actual steps, know what radicals were involved, and have no doubts as to the validity of the mechanism.

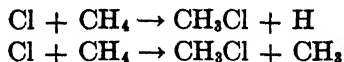
The photochlorination of methane illustrates this very nicely. The over-all reaction rate shows a dependence (7) on methane, oxygen, and chlorine concentrations which makes it seem certain that the reaction occurs through an atom or radical intermediate similar to that of the Nernst chain mechanism for the hydrogen-chlorine reaction. There are, however, two quite different mechanisms which give the dependence found experimentally, one involving hydrogen atoms as the chain carrier and the other involving methyl groups:



Both of these give the rate as follows:

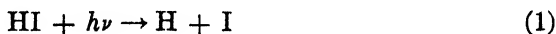
$$\frac{d(\text{HCl})}{dt} = \frac{K[\text{CH}_4][\text{Cl}_2]}{k[\text{O}_2] + [\text{Cl}_2]}$$

in good agreement with experiment if  $k$  be put equal to unity. Thus the whole question of which of the two postulated mechanisms is valid depends upon the relative rates of the two reactions of chlorine atoms and methane:



A knowledge of these two reaction rates would allow us to choose between the two over-all mechanisms, even though we should not know the values of the rate constants of the other steps in the process. When we are faced with a dilemma of this type the obvious solution would seem to be to attempt to discover these needed values from some other source. In the present example this has not been found possible, but there are cases which should lend themselves to this type of solution.

Since hydrogen atoms occur in so many of the photoreactions which have been studied, it is quite natural to find the same processes involving these atoms appearing in different reactions. Here it is quite possible to obtain values of the same reaction constant from different sources, and in some cases a fair agreement may be found. However, extremely serious discrepancies exist which should claim our attention. The ideal coordination of the reaction constant values should be obtained by basing the values of the reaction constants involving hydrogen atoms upon some well established, or easily determined constant. In attempting to do this in connection with some recent results on hydrogen iodide photooxidation rather startling difficulties are observed. Let us take a simple example,—the photodissociation of hydrogen iodide. The physicist has already informed us that the first process is dissociation of the molecule by the light quantum:



What possible reactions may then occur?



If it were known *a priori* that reactions 3, 4, 5, and 6 were slow compared to reaction 2, we should have full knowledge that only reactions 1, 2, and 4 were involved, as is found experimentally. There are theoretical bases for this result. The last three are association reactions and reaction 3 is highly endothermic. But if we were to attempt to find accurate values for the rate constants there would be considerable difficulty. Certainly from the above reaction nothing quantitative can be learned of these values. If, however, iodine vapor be present in the system we may determine the relative values of the two reactions  $\text{H} + \text{HI}$  and  $\text{H} + \text{I}_2$ , since by a study of the inhibiting effect of iodine the ratio of the two constants may be obtained. This has been done by Bonhoeffer and Farkas, who found

$$\frac{k_{\text{H}+\text{I}_2}}{k_{\text{H}+\text{HI}}} \quad 100$$

The value of  $k_{\text{H}+\text{I}_2}$  is not known experimentally, but may be calculated on the rather reasonable assumption that the reaction goes on every collision.

It is now also possible to compare the two constants  $k_{\text{H}+\text{HI}}$  and



$k_{\text{H}+\text{O}_2+\text{M}}$  by illuminating mixtures of hydrogen iodide and oxygen. From this may be obtained the ratio (3, 5)

$$\frac{k_{\text{H}+\text{O}_2+\text{M}}}{k_{\text{H}+\text{I}_2}}$$

and if the  $k_{\text{H}+\text{I}_2}$  be computed on the basis of reaction on every collision a value of  $k_{\text{H}+\text{O}_2+\text{M}}$  is obtained. Such a value has also been calculated roughly by Bodenstein (2, 4) from data on the hydrogen-chlorine reaction and found to agree with that as obtained above.

In spite of this agreement, and because the standard of  $k_{\text{H}+\text{I}_2}$  used is perhaps a shaky one, it is obviously worthwhile to seek a more certain, and an experimentally determined constant to which to refer our values. Farkas and Sachsse (6) have furnished us with a value of the ratio

$$\frac{k_{\text{H}+\text{O}_2}}{k_{\text{H}+\text{H}+\text{H}_2}}$$

which allows of comparison with perhaps the most logical of the reaction constant standards for reactions involving hydrogen atoms, the recombination process. This has been the subject of work by Smallwood (9), Steiner (10), Senftleben (8), Farkas and Sachsse (6), and Amdur (1). However, the results are sadly conflicting. Smallwood and Amdur find that the recombination occurs through a three atom process, while Steiner and Farkas and Sachsse find that the molecule is the more efficient third body. The result of this is that Steiner gives for  $k_{\text{H}+\text{H}+\text{H}_2} = 1 \times 10^{16}$  cc.<sup>2</sup> mole<sup>-2</sup> sec.<sup>-1</sup> and Smallwood  $3 \times 10^{14}$ . Farkas and Sachsse, using a competitive reaction method involving ortho-para hydrogen conversion, obtain  $3 \times 10^{16}$ . As we have said, the latter also determined by the same method the relative values of  $k_{\text{H}+\text{H}+\text{H}_2}$  and  $k_{\text{H}+\text{O}+\text{H}_2}$ . Since the relative values of  $k_{\text{H}+\text{HI}}$  and  $k_{\text{H}+\text{O}_2+\text{M}}$  are known from the effect of oxygen on the hydrogen iodide decomposition, it is possible to compare the validity of choosing  $k_{\text{H}+\text{I}_2}$  as a standard with that of the constant of atom recombination. The result is highly unsatisfactory, no matter which value of the atom recombination constant is used. The discrepancy varies from a factor of 100 in the case of Farkas and Sachsse to  $10^4$  for Smallwood's value. Certain reasons for some difference can be seen, but such large ones are not easy to explain.

In conclusion, it should be emphasized that the accurate determination of these and other atom and radical reaction constants seems to be one of the most pressing and profitable fields for future efforts. It might even be said, perhaps too optimistically, that a correlation of such constants would have the same relation to the photochemistry of the gaseous state that the accurate atomic weight determinations had to all of chemistry.

## REFERENCES

- (1) AMPUR: J. Am. Chem. Soc. **57**, 856 (1935).
- (2) BATES: Proc. Nat. Acad. Sci. **19**, 81 (1933).
- (3) BATES AND LAVIN: J. Am. Chem. Soc. **55**, 81 (1933).
- (4) BODENSTEIN: Trans. Faraday Soc. **27**, 413 (1932).
- (5) COOK AND BATES: J. Am. Chem. Soc. In press.
- (6) FARKAS AND SACHSSE: Z. physik. Chem. **27B**, 111 (1934).
- (7) JONES AND BATES: J. Am. Chem. Soc. **56**, 2282 (1934).
- (8) SENFTLEBEN AND RIECHEMEIER: Ann. Physik **6**, 105 (1930).
- (9) SMALLWOOD: J. Am. Chem. Soc. **56**, 1547 (1934).
- (10) STEINER: Z. physik. Chem. **15B**, 249 (1932).

## DISCUSSION

DR. R. A. OGG, JR. (Stanford University): Aside from the disagreement among various investigators as to the velocity of hydrogen atom recombination, it appears that the discrepancy pointed out by Professor Bates is readily explained. In essence, the ratios

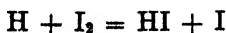
$$\frac{k_{H+I_2}}{k_{H+HI}}, \frac{k_{H+HI}}{k_{H+O+M}}, \text{ and } \frac{k_{H+O+M}}{k_{H+H+M}}$$

have been determined experimentally. The product of these three gives the ratio

$$\frac{k_{H+I_2}}{k_{H+H+M}}$$

If this ratio and the measured value of  $K_{H+H+M}$  be multiplied, a *calculated* value of  $K_{H+I_2}$  is found which is *smaller* than that based on the assumption of reaction occurring at every collision. The simplest inference to be drawn from the discrepancy is that the assumption of reaction on every collision between H and  $I_2$  is unwarranted, and that this reaction actually requires a finite, although doubtless small, activation energy. This conclusion seems the more reasonable, in view of the fact that the closely related reaction  $H + Br_2$  apparently requires an activation energy of some 3000 calories per mole. (Kassel, L. S.: Kinetics of Homogeneous Gas Reactions. The Chemical Catalog Co., New York (1932)). The observed discrepancy could actually be used to estimate the activation energy for  $H + I_2$ , but the uncertainty in the value of  $k_{H+H+M}$  would be reflected in a corresponding uncertainty of this activation energy.

DR. LOUIS S. KASSEL (U. S. Bureau of Mines, Pittsburgh): The calculation actually made by Eyring for the reaction

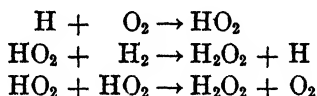


applies only when the atom approaches along the axis of the molecule. For other directions of approach a small activation energy is a conceivable result of the as yet unmade calculation. Should such a result be found, theory would give a steric factor which might be of the order of  $10^{-1}$ .

PROFESSOR BATES: In reply to the remarks of Drs. Ogg and Kassel, it perhaps can be said that Dr. Kassel's remark is really an answer to Dr. Ogg's explanation. We might expect a small steric or activation energy factor to produce a discrepancy of an order of magnitude, but not one which apparently has a possible minimum value of about 300-fold. The fact that  $H + Br_2$  has an activation energy of 3000 calories does not insure that  $H + I_2$  have one. In fact, calculations which give  $H + Br_2$  this value yield a value of zero for  $H + I_2$ .

PROFESSOR J. FRANCK (Johns Hopkins University): Could I have detailed information about the reaction between hydrogen and oxygen? I should like to know how far chain reaction in this case plays a rôle.

PROFESSOR BATES: The mechanism which I believe to be the correct one is



The reasons which lead to this conviction are too many and too long to be presented here, but are set forth in a paper published in the Journal of Chemical Physics in 1933.

PROFESSOR W. H. RODEBUSH (University of Illinois): I do not believe that the data in the literature on the recombination of hydrogen atoms are reliable. I feel that we have a method for the measurement of atom combination developed to a point where it should be possible to determine the rate of recombination of hydrogen atoms accurately.

DR. J. A. LEERMAKERS (Eastman Kodak Co., Rochester) (communicated): In connection with Dr. Bates' remarks, it seems to me worth while to mention a reaction for which a mechanism has been derived which has found support from three independent sets of measurements. I refer to the decomposition of acetaldehyde. Rice and Herzberg first postulated a chain mechanism which involved methyl radicals for the purely thermal decomposition of acetaldehyde. Hinshelwood and coworkers were responsible for the measurements which were made on the pure vapor. Allen and Sickman later sensitized the acetaldehyde reaction by thermally decomposing azomethane, which has been shown to give methyl radicals, in a system containing both azomethane and acetaldehyde; the mechanism of Rice and Herzberg was found to fit the experimental facts entirely satisfactorily. I studied the kinetics of the photolysis of acetaldehyde at

moderately high temperatures, and found that the original mechanism of Rice and Herzberg, with insignificant changes, accounted for the experimental data.

These three series of measurements, the purely thermal, the thermally sensitized, and the photochemically sensitized decomposition of acetaldehyde, tie together so well that it seems highly probable that the single mechanism is correct.

There are numerous experiments of the type I have mentioned which can be made on the decompositions of organic compounds, and I feel that such studies will lead to a very definite understanding of the mechanism of such reactions. At least such studies will automatically eliminate from consideration many mechanisms which fit one set of facts alone.

DR. OGG (communicated): From Professor Bates' last remarks it would appear that the assumption of a zero activation energy for  $\text{H} + \text{I}_2$  rests solely upon the calculations of Eyring. The discrepancy is therefore between the results of these calculations and of experiment. Since the inception of the London-Eyring-Polanyi treatment of adiabatic reactions it has become increasingly clear that this treatment, while undoubtedly correct in principle, involves such serious approximation that absolute values of the calculated activation energies are not reliable to within several thousand calories per mole. Hence Eyring's calculated "zero activation energy" for the reactions  $\text{H} + \text{Cl}_2$ ,  $\text{H} + \text{Br}_2$ , and  $\text{H} + \text{I}_2$  is to be interpreted as indicating the respective activation energies to be small, but not necessarily zero. It is of interest to note that for each of these reactions the experimentally determined velocity suggests an activation energy of the order of 2000 to 3000 calories per mole,—the experimental evidence in the case of  $\text{H} + \text{I}_2$  being that offered by Professor Bates himself. It is the writer's opinion that no adiabatic reaction proceeds without inertia, and the above evidence supports this view. It is of interest to contrast the above reactions with those of sodium atoms and halogens,  $\text{Na} + \text{Cl}_2$ ,  $\text{Na} + \text{Br}_2$ , and  $\text{Na} + \text{I}_2$ . These latter reactions have been definitely proved to require a negligibly small activation energy, and it is believed that this fact arises from the non-adiabatic mechanism which obtains, as contrasted to the adiabatic mechanism of the hydrogen atom-halogen reactions.



# THE REACTION BETWEEN NITRIC OXIDE AND ATOMIC OXYGEN

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The scarcity of chemiluminescent reactions has been noted by many observers. There appear to be almost no reactions known in which there is a stoichiometrical relation between the light emitted and the chemical reaction. Often there is only one quantum of light emitted for a very large number of reacting molecules, so that one may not be sure that he has observed the reaction which produces the light emission at all. It could not be expected, of course, that reactions in, or at the surface of, condensed phases would be particularly efficient, since collisions of the second kind might be expected to convert much of the energy of excitation into thermal energy before it could be radiated. The condition most favorable to chemiluminescence is, therefore, to be found in a gas at low pressures, and it is under these conditions that the "afterglow" reactions take place.

The similarity between the conditions necessary for an afterglow, and the conditions prevailing in the nebulae and in auroral discharges has been recognized for a long time by physicists.

The simplest chemiluminescent process is the formation of a molecule in an excited electronic state from molecules or atoms in a normal state. By the term "normal state" we mean to rule out excited or even metastable electronic states of molecules or atoms, since such do not have a sufficiently long life to participate in chemical reaction under ordinary conditions. It may, of course, be argued from the chemist's standpoint that atomic oxygen is itself in an excited and ephemeral state.

Speelman and the author were led, from some observations made on the nitrogen afterglow, to suspect that the reaction between nitric oxide and atomic oxygen was of this character. A simple experiment demonstrated that, when nitric oxide is mixed with atomic oxygen at low pressures, the reaction



takes place accompanied by a greenish-white luminescence, which is of considerable intensity when approximately equivalent amounts of the

reacting substances are present. This afterglow is not of sufficient intensity to photograph readily with a spectrograph of high dispersion, but when photographed with a Bausch and Lomb quartz spectrograph a series of diffuse, poorly resolved bands were obtained which extended throughout the visible spectrum with maximum intensity at about 5000 A.U. This spectrum appears to correspond to that observed by Strutt (Lord Rayleigh) (5), which has been designated by Stoddard (4) as the oxygen afterglow. The idea that nitric oxide was involved in the reaction producing this afterglow is, of course, not new. Strutt supposed that the reaction was between nitric oxide and ozone. When he attempted to prove this he was not able to get an afterglow with ozone made at atmospheric pressure, but he did get a chemiluminescent flash when nitric oxide was admitted to a trap in which ozone had been condensed with liquid air. Apparently Strutt did not realize that oxygen might be dissociated into atoms by the discharge at low pressures.<sup>1</sup>

The chemical proof that reaction 1 produces the luminescence is necessarily a process of elimination. There are a number of reactions possible between oxygen and the oxides of nitrogen, and an account of the study of these has been published elsewhere (3). It suffices to say that the reaction above is the only one that appears to take place, to an appreciable extent, under all circumstances in which the greenish-white afterglow is observed.

According to Mecke (1), nitrogen dioxide, when illuminated with light of wave length about 3700 A.U., decomposes by a predissociation process into nitric oxide and atomic oxygen, both species in the normal state. Reaction 1 therefore satisfies our criterion for a chemiluminescent reaction, viz., the formation of a molecule in an excited electronic state from atoms or molecules in the normal state. This process is not likely to take place in bimolecular collisions, of course, because the life of the complex is only the duration of the collision, which is very short compared to the time required for the emission of a photon. Accordingly, we must assume that

<sup>1</sup> The whole matter has been confused by the publication of a note by Lord Rayleigh (Proc. Roy. Soc. London **150A**, 34 (1935)) in which he asserts that the ozone plus nitric oxide reaction produces the yellow afterglow characteristic of nearly pure nitrogen, and that oxygen containing no other impurity than water gives a white afterglow.

The yellow afterglow consists of the first positive bands of nitrogen, and this afterglow can be produced in nitrogen which contains no oxygen in any form. It is, of course, difficult to purify moist oxygen to a point where there is no afterglow, but it is possible to reduce the afterglow so much that it is scarcely visible in a darkened room, and one may suspect that this afterglow is due to traces of nitric oxide. It should be noted that the reaction between ozone and nitric oxide liberates only 48 calories of energy, which correspond to a short wave length limit of 5900 A.U.

reaction 1 takes place by triple collision with the loss of enough energy to stabilize the molecule. Provided further collisions do not occur within a period of  $10^{-8}$  seconds, the residual excitation energy of the molecule will be radiated. At higher pressures this energy would probably be dissipated by collision, but it is, of course, difficult to produce atomic oxygen at higher pressures to test this prediction.

The varying amounts of energy lost in the triple collisions account for the widely distributed range of frequencies radiated. Were it not for this dissipation of energy, one would expect uniform radiation of wave length about 3700 A.U. The luminescence observed corresponds to the fluorescence observed by Norrish (2) when nitrogen dioxide is illuminated with light of wave length too short to produce dissociation. Nitrogen dioxide is a nonlinear molecule, and its absorption spectrum has not been analyzed. It is, therefore, not possible at present to identify the afterglow spectrum positively as belonging to nitrogen dioxide.

The duration of the afterglow is greatly decreased by increasing the pressure. At 1 mm. the afterglow disappears completely in about one second. This dependence upon pressure agrees with the hypothesis of triple collisions, although quantitative measurements are yet to be made.

The chemiluminescent efficiency of reaction 1 is probably quite high, but a large amount of energy is dissipated in the production of atomic oxygen. A more interesting property of the luminescence is that its spectral intensity distribution appears to approximate that of sunlight. Sufficient intensity has not been obtained, however, to make possible a test of its value as a source of illumination.

#### REFERENCES

- (1) MECKE: *Z. physik. Chem.* **7B**, 108 (1930).
- (2) NORRISH: *J. Chem. Soc.* **1929**, 1611.
- (3) SPEALMAN AND RODEBUSH: *J. Am. Chem. Soc.* **57**, 1474 (1935).
- (4) STODDARD: *Proc. Roy. Soc. London* **147A**, 464 (1934).
- (5) STRUTT: *Proc. Phys. Soc. London* **23**, 66 (1910).

#### DISCUSSION

DR. OGG: Phenomena similar to that described by Professor Rodebush have been previously observed in the formation of diatomic molecules from atoms. Bonhoeffer and Pearson (*Z. physik. Chem.* **14B**, 1 (1931)) observed an intense emission of the band spectrum of OH molecules on mixing oxygen atoms and hydrogen atoms. Gaviola and Wood (*Phil. Mag.* [7] **6**, 1191 (1928)) similarly found an emission of the band spectrum of NH in a system containing nitrogen atoms and hydrogen atoms. The electronic band spectra of OH and NH molecules have been shown by



Bates (*Z. physik. Chem.*, Bodenstein Festband, p. 329 (1931)) to be of the predissociation type. Since the electronic band spectrum of  $\text{NO}_2$  also shows predissociation, it is probable that the emission of the  $\text{NO}_2$  bands from oxygen atoms and NO molecules is a process entirely parallel to those cited.

PROFESSOR BATES: Professor Rodebush's results are in accord with the fluorescence of  $\text{NO}_2$  observed by Norrish some years ago. He found that the fluorescence occurred only in those spectral regions where the quantum yield was less than the expected value of two.

# THE CORRELATION OF PHOTOCHEMICAL REACTIONS IN GASES WITH THOSE IN SOLUTION<sup>1</sup>

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Developments in the interpretation of atomic and molecular spectra have been useful to photochemistry primarily in connection with gaseous reactions. For it is ordinarily only in the gaseous state that substances give sufficiently detailed spectra to permit of precise interpretation; an absorption spectrum which is discrete in the gaseous state usually becomes continuous in a condensed state or in solution. Furthermore, the formulas of kinetic theory which are needed in the discussion of reaction kinetics have had a sounder basis in their application to gases than to liquids. It is natural, then, that in treating solution reactions, free use has been made of information concerning gaseous substances. In view of this, it appeared to be of interest to review such existing data as permit comparison of photochemical processes in gases with those in liquids. A major part of the present survey consists in the comparison of data in cases where the same reaction has been studied in gas and in solution, especially in inert solvents.

Photochemical reactions are conveniently considered to involve two types of process: (1) those primary processes accompanying the absorption of radiation, and (2) those subsequent secondary processes which proceed without the further intervention of radiation. Consequently it will be convenient here to consider the effect of solvent on these processes separately.

In general, substances exhibit in solution absorption spectra which differ from those given in the gaseous state even aside from the broadening of absorption lines in solution; for example, the maximum visible absorption of iodine in alcoholic solution is in the blue, while that for gaseous iodine is near the green. However, with inert non-polar solvents or with inert solvents which are similar to the solute, the alteration is often relatively slight. When mercury is dissolved in hexane, although the first resonance line is considerably broadened (5) and separated somewhat into two components, nevertheless the absorption still occurs in the immediate

<sup>1</sup> Contribution No. 500 from the Gates Chemical Laboratory.

neighborhood of the frequency of the gaseous line 2537; furthermore, the integral absorption coefficient in the solution is little different from that in the gas (33). The unchanged position of the absorption shows that the difference between the energies of an excited and a normal mercury atom is the same in solution as in gas; equality of the integral absorption coefficient signifies equal probability of electronic transition. Further examples of both qualitative and quantitative similarity in absorption spectra in the gaseous state and in solution are afforded by the halogens in carbon tetrachloride, chloroform, and carbon bisulfide, by hydrogen peroxide (41) in water, and by hydrogen sulfide (26) in water and in hexane.

When such similarity between the gaseous and solution absorption spectra exists, it is reasonable to assume that absorption is accompanied by the same electronic transition in both cases. In spite of this, the outcome of the absorption process may be considerably modified in solution. If the gaseous absorption is discrete and results in an excited molecule, then in solution the excited molecule may either (1) have its excitation energy degraded to thermal motion by collision with solvent molecules, or (2) dissociate on collision with solvent molecules if its energy be sufficient. (If the solvent be not inert, there exist further possibilities of reaction with it.) If the gaseous absorption is continuous and results in dissociation, then in solution collision with a solvent molecule before dissociation is completed may remove energy to prevent its occurrence. Even if dissociation does occur, there is in solution an increased probability of immediate recombination of the same dissociating partners resulting from the short mean free path, which leaves them initially in close proximity. This last process has been discussed by Franck and Rabinowitsch (19), and has been called by them "primary recombination" to distinguish it from the "normal" uniting of particles which were not previously partners. Similar possibilities exist if the gaseous absorption is in a predissociation region; here, however, opportunity for deactivation is increased by the longer interval before dissociation, especially with polyatomic molecules (20).

In order to obtain some idea of what to expect of the effect of solvent on processes subsequent to those mentioned, we may look to the results obtained with purely dark reactions. In general the rates and temperature coefficients of ordinary reactions in solution are considerably dependent upon the solvent used, and this dependence is highly specific and in large measure unpredictable. Nevertheless, Moelwyn-Hughes, who has extensively reviewed this field (28), has concluded that with inert non-polar solvents, such as carbon tetrachloride, rates and temperature coefficients not very different in gas and in solution may be expected, and that the application of gas kinetic theory collision rates to solutes may be made with some confidence.

One type of reaction step, namely the bimolecular association of atoms, may be expected to proceed much more rapidly in solution, for the co-operation of a third colliding body is necessary in order to give rates of importance. When the molecule resulting from a bimolecular association contains a sufficient number of atoms, then, as Kassel has shown (25), the necessity for a third body to stabilize the collision is no longer present. In this case, grounds for predicting a more rapid association in solution are absent.

After this outline of some effects which may be expected, individual cases, for which data are given in table 1, will now be considered. It may be well to summarize at the outset and say that for those cases for which data are available, where the same reaction proceeds in the gas and in solution or liquid, it proceeds with about the same quantum yield or same specific rate in each or else proceeds more rapidly in the gas.<sup>2</sup> It is usually difficult to be certain just which dissipational effect preponderates in any individual case.

Nitrogen dioxide shows a predissociation spectrum, the products of the predissociation being presumably NO and O (both normal). It shows a photochemical threshold (10, 30) approximately at the predissociation limit, with no decomposition in the band region and quantum yields of about two NO<sub>2</sub> decomposed per quantum (products: 2NO and O<sub>2</sub>) in the ultra-violet. In gaseous mixtures with nitrogen pentoxide, the net result of illumination is sensitized decomposition of the nitrogen pentoxide; and this may be regarded simply as the usual decomposition of nitrogen dioxide followed by rapid reaction of nitric oxide with nitrogen pentoxide (3, 22). In carbon tetrachloride solution the decomposition is relatively small (22).

It is interesting to compare the behavior of chlorine dioxide with that of nitrogen dioxide. Gaseous chlorine dioxide shows bands with fine structure extending from the green into the ultra-violet; the bands become diffuse at 3750 A.U., and this is attributed to predissociation. In carbon

<sup>2</sup> Note added September 4, 1935: Dr. R. A. Ogg, Jr., has kindly called the writer's attention to one case where existing data are not in agreement with this generalization. At wave lengths corresponding to the continuous absorption of ethyl iodide, gaseous ethyl iodide undergoes very little decomposition, whereas a considerably greater production of free iodine has been found with liquid ethyl iodide and with ethyl iodide in hexane and in benzene solution. This case is discussed at length by West and Ginsburg (WEST, W., AND GINSBURG, E.: J. Am. Chem. Soc. **56**, 2626 (1934)).

It has been contended (STOBBE, H., AND SCHMITT, P.: Z. wiss. Phot. **20**, 57 (1920)) that this iodine production is due to oxidation. Although recent investigators have not ignored the possible effect of oxygen here, one might, in view of the exceptional nature of this case, wish for experiments in which rigorous exclusion of oxygen and water was assured.

TABLE 1

*Quantum yields of reactions in gaseous and condensed systems*

REACTION	WAVE LENGTH	QUANTUM YIELDS		
		Gas	CCl <sub>4</sub>	
$\text{N}_2\text{O}_5 \rightarrow \text{NO}_2 + \frac{1}{2}\text{O}_2$ (sensitized by $\text{NO}_2$ )	4358	0		
	4050	0.7	0.03	
	3660	1.8	0.02(0.15)	
	3130	1.9		
$2\text{ClO}_2 \rightarrow \text{Cl}_2 + 2\text{O}_2$		Gas	CCl <sub>4</sub>	Water
	3000		2.1	1.0
	3130	(Much $\text{ClO}_2$ formed; chains)		
	3665		2.2	0.76
	4050		2.2	0.50
	4358		1.0	0.20
$2\text{Fe}(\text{CO})_5 \rightarrow \text{Fe}_2(\text{CO})_9$ + CO		Gas	Liquid	
	2540		1.89	
	3000		1.86	
	3660		1.76	
	4050	2.32		
	4358		1.66	
$2\text{HI} \rightarrow \text{H}_2 + \text{I}_2$		Gas	Liquid	Hexane (0.8 molal)
	2070	1.98		
	2220			1.52
	2530	2.08		
	2820	2.06		1.78
	3000		1.84	
$\text{H}_2\text{S} \rightarrow \text{H}_2 + \text{S}$		Gas	Hexane	Water (0.115 molal)
	2070	2.1	0.97	0.43
	2200		0.95	0.32
	2530			0.23
$\text{N}_2\text{O}_5 \rightarrow 2\text{NO} + \frac{1}{2}\text{O}_2$		Gas	CCl <sub>4</sub>	
	2800	0.6	0.04	
	2650	0.6	0.05	
		Gas	CCl <sub>4</sub>	
$2\text{Cl}_2\text{O} \rightarrow 2\text{Cl}_2 + \text{O}_2$ (also $\text{ClO}_2$ )	2537	4.5		
	3130	3.5		
	3650	3.4		
	4358	3.2	1.8	

TABLE 1—*Concluded*

REACTION	WAVE LENGTH	QUANTUM YIELDS			
		Gas	Liquid	Water	Hexane
$2\text{NH}_3 \rightarrow \text{N}_2 + 3\text{H}_2$	~2100	0.14 to 0.25	No decomposition	No decomposition	Little $\text{NH}_3$ decomposition. Sensitized decomposition of hexane
$\text{C}_2\text{Cl}_4 + \text{Cl}_2 \rightarrow \text{C}_2\text{Cl}_6$	4358	Chains dependent on $(\text{Cl}_2)$ and $(I_{\text{abs}})$ but about same in gas and $\text{CCl}_4$			
$\text{C}_2\text{Cl}_4$ oxidation (sensitized by $\text{Cl}_2$ )	4358	Gas		$\text{CCl}_4$	
		~375 at 0.01 atm.		~1 at 0.04 m.	
$\text{CHCl}_3$ oxidation (sensitized by $\text{Cl}_2$ )	4358	Gas		$\text{CCl}_4$	
		~100 at ~0.1 atm.		~0.6 at 0.05 m.	

tetrachloride solution decomposition simply into  $\text{Cl}_2$  and  $\text{O}_2$  occurs with quantum yields (7, 29) of 2 at 4150 A.U. and less and 1 at 4358 A.U. At least at the shorter wave lengths, primary deactivation by solvent apparently does not occur, unless the yield of 2 be regarded as fortuitous. In the gaseous state, chain reaction with the formation of  $\text{ClO}_2$  occurs (37). In aqueous solution the solvent is not inert, and  $\text{HCl}$  and  $\text{HClO}_2$  are formed (7).

Another substance showing a predissociation spectrum is ammonia; the absorption process is interpreted as resulting in  $\text{NH}_2$  and  $\text{H}$ . However, at room temperature only about 0.25  $\text{NH}_3$  or less is decomposed per quantum (31). Various experiments have led to the belief that the lowness of the yield is due, at least in part, to re-formation of  $\text{NH}_3$  from  $\text{H}$  and  $\text{NH}_2$  or  $\text{N}_2\text{H}_4$ ; the most recent of these experiments involves the photolysis of ordinary ammonia in the presence of atomic deuterium with the formation of deuterio-ammonias (39). In the pure liquid state, ammonia suffers no appreciable decomposition (31), nor does it do so in aqueous solution (17). In hexane solution little decomposition of ammonia results, but instead an ammonia-sensitized decomposition of the hexane (17). It has been assumed that in this case the ammonia is deactivated before dissociating, its energy serving to decompose the hexane.

Iron pentacarbonyl,  $\text{Fe}(\text{CO})_5$ , is decomposed in the gaseous state into carbon monoxide and diferro-nona-carbonyl,  $\text{Fe}_2(\text{CO})_9$ , with a quantum

yield (16) of about  $2\text{Fe}(\text{CO})_5$ . In the pure liquid state yields (46) only a few per cent smaller have been found.

A well-known reaction in which the gaseous absorption is clearly continuous is the decomposition of hydrogen iodide. In the gas two molecules of hydrogen iodide are decomposed per quantum absorbed (43). There is little doubt that the gaseous decomposition proceeds through the reactions:



Pure liquid hydrogen iodide decomposes with substantially the same quantum yield (4) and may be supposed to do so by the same mechanism. If, however, owing to the frequency of collision with other hydrogen iodide molecules in the liquid, the reaction forming  $\text{H}_2$  be supposed to occur before the completion of dissociation, a formally different mechanism may be written (19):



In hexane solution lower values, 1.2 to 1.8, dependent on the wave length and somewhat on the concentration, have been obtained (44). These lower values are possibly due to either deactivation or primary recombination, although it is not clear why either of these processes should lead to a concentration effect in dilute solution. Normal recombination of hydrogen atoms could lead to a concentration effect, and could also lead to lower quantum yields at the shorter wave lengths, where the absorption coefficient of hydrogen iodide is larger and the local concentration of hydrogen atoms produced with a given intensity is higher.

Gaseous hydrogen sulfide similarly has a continuous absorption. Whether the absorption process is accompanied by dissociation into  $\text{H}_2$  and S or into H and HS is not certain ( $2\text{H} + \text{S}$  is not energetically possible). At pressures of 250 mm. or less, two molecules of hydrogen sulfide are decomposed per quantum (38), and with either primary products this yield could result from a mechanism analogous to that for hydrogen iodide decomposition. At higher pressures, yields of 3 to 4 have been found but not very satisfactorily accounted for. In hexane solution yields of close to 1 have been found, with no evident concentration or wave length dependence (45). Unless this value of unity be regarded as accidental, it is most readily accounted for as resulting from complete normal recombination of H atoms (or of S atoms) with solvent molecules as third bodies. In aqueous solution the quantum yields are still smaller, and decrease with increasing wave length.

Only continuous absorption starting at 3050 A.U. has been found (42) with gaseous nitrogen pentoxide. This long wave limit corresponds closely to the energy change in the reaction  $\text{N}_2\text{O}_5 \rightarrow 2\text{NO}_2 + \text{O}$ . The quantum yield (22) of gaseous decomposition is, however, only 0.6. This is difficult to account for with the above primary process; for if reoxidation of  $\text{NO}_2$  by O occurs here, it is not evident why it should not do so in the decomposition of  $\text{NO}_2$ . A rather large depression of the yield occurs in carbon tetrachloride solution (22).

Another substance whose gaseous absorption is continuous is chlorine monoxide. The gaseous photochemical decomposition gives  $\text{Cl}_2$ ,  $\text{O}_2$ , and small amounts of  $\text{ClO}_2$  and other oxides. The more recent values of the quantum yields (18, 35) are 3.2 to 3.5  $\text{Cl}_2\text{O}$  decomposed at the longer wave lengths and 4.5  $\text{Cl}_2\text{O}$  at 2537 A.U. At the longer wave lengths the quantum yields remain unchanged when chlorine instead of chlorine monoxide is the primary absorber. In view of this fact, secondary decomposition by chlorine atoms evidently occurs. The numerical values of the quantum yields suggest also short-chain decomposition. In carbon tetrachloride solution the yields are somewhat smaller (12), and these smaller values have been attributed (18) to the effect of solvent in stabilizing chain-breaking steps.

In view of the photochemical importance of the halogens, it is of especial interest to know the products of the absorption process under various circumstances. When the absorption corresponds to the continuum, there is little doubt that atoms result, although these may be subject to a certain amount of primary recombination in solution. However, the fact that the chlorine-sensitized decomposition of ozone occurs in carbon tetrachloride solution with yields (8) of close to 2 suggests that primary recombination is not large in this particular case.

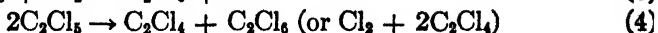
The chlorination of tetrachloroethylene has been studied both in gas (11) and solution (27) with the wave length 4358 A.U., which lies in the gaseous continuum. In the gaseous state the local rate of reaction is given by

$$-\frac{d(\text{Cl}_2)}{dt} = k(I_{\text{abs}})^{\frac{1}{2}}(\text{Cl}_2)$$

Quantum yields (dependent on  $(\text{Cl}_2)$  and  $(I_{\text{abs}})$ ) of several hundred have been measured. The value of  $k$  has been found to be  $147 \text{ einsteins}^{-\frac{1}{2}} \times \text{cm.}^{\frac{1}{2}} \times \text{sec.}^{-1}$  at  $26^\circ\text{C}$ . In carbon tetrachloride solution a rate expression of the same form is found when sufficient tetrachloroethylene is present, and the value of  $k$  is 165 at  $22^\circ\text{C}$ . The value of  $k$  for the gas is subject to some uncertainty, but can hardly be greatly different from that



for the solution. A simple chain mechanism which is in agreement with these facts is:



With long chains, this leads to the empirical rate expression with  $k = k_3/k_4$ . The rate-determining reactions are accordingly reactions 3 and 4, and since these are not bimolecular associations, there is no ground for predicting a solvent effect on either.

When oxygen is present in addition to chlorine and tetrachloroethylene, oxidation instead of chlorination occurs, the products being trichloroacetyl chloride and some phosgene. In this case the rate is proportional to the first power of the light intensity, and in the gas long chains again occur (11). In solution the chains are several hundredfold shorter (13). Since the elementary absorption process is presumably the same as in the absence of oxygen, the different effect of solvent in the chlorination and in the oxidation clearly lies in the subsequent processes; for the oxidation, these are not well understood. In the chlorine-sensitized oxidation of chloroform, long chains in the gas but not in carbon tetrachloride solution are also found (9).

When an excited halogen molecule is produced by a wave length of the band region, it may still possess sufficient energy for dissociation into normal atoms; and either this or deactivation may occur when the excited molecule enters into collision. In the case of bromine, indirect evidence that dissociation, instead of degradation to thermal energy, occurs both in the gaseous state and in solution is furnished by a number of photochemical reactions. In the gaseous state several reactions have been found to proceed with substantially the same yield with wave lengths on either side of the convergence; among these are the formation of hydrogen bromide (23), the bromination of cyclohexane (24), the bromination of acetylene (6), and the bromine-sensitized decomposition of chlorine dioxide (36, 37). In the liquid state, yields only slightly smaller on the long-wave side than on the short have been reported in the bromination of cinnamic acid in carbon tetrachloride solution (2) and in the bromination of liquid benzene (32); in the bromination of maleic ester and its rearrangement to fumaric ester, yields about half as large at 5461 A.U. as at 4358 A.U. have been found (15).

For gaseous iodine there is direct evidence that at least some iodine atoms result when the gas is illuminated by wave lengths longer than 5100 A.U. in the presence of argon, for under these circumstances absorp-

tion lines due to atomic iodine appear in the ultra-violet (40). For iodine in solution, the data are not concordant. In the iodine-sensitized rearrangement of *allo*-cinnamylidene acetic acid into the normal form, 5461 A.U. has been reported (21) as more effective than 4358 A.U. both in benzene and in carbon tetrachloride solution; this appears inexplicable and invites re-examination. In the iodine-sensitized decomposition of ethylene iodide in carbon tetrachloride solution, quantum yields only one-fifth as great for 5461 A.U. as for 4358 A.U. have been measured (34); the conclusion drawn from this result was that the excited iodine molecule usually lost its energy on collision with solvent molecules. However, in view of the fact that this reaction proceeds at a rate proportional to the square root of the intensity of illumination, ordinary measurement of quantum yield alone does not permit such a conclusion, for when the rate of a reaction is not proportional to the intensity, the over-all quantum yield depends on the distribution (1) of radiation through the reacting medium, and this distribution changes in general with the absorption coefficient. With due allowance for this fact, the effect of wave length on the sensitized ethylene iodide decomposition has recently been remeasured (14). With local rates of reaction represented by

$$\frac{d(I_2)}{dt} = k(I_{abs})^{\frac{1}{2}}(C_2H_4I_2)$$

values of  $k$  in carbon tetrachloride solution at 76.6°C. were found to be 0.425 einstein<sup>-1</sup> × cm.<sup>1</sup> × sec.<sup>-1</sup> at 4358 A.U., 0.396 at 5461 A.U., and 0.368 at 5780 A.U. If  $\beta$  be the fraction of the absorbed quanta which result in dissociation of iodine molecules, directly or on subsequent collision, then for two different wave lengths

$$\beta_1/\beta_2 = k_1^2/k_2^2$$

and

$$\beta_{4358}:\beta_{5461}:\beta_{5780} = 1:0.87:0.75$$

It appears then that with iodine, wave lengths corresponding to the band region are little less effective than those of the continuum in producing dissociation in carbon tetrachloride solution.

#### REFERENCES

- (1) ALLMAND, A. J.: J. Chem. Soc. **1929**, 1557.
- (2) BAUER, W. H., AND DANIELS, F.: J. Am. Chem. Soc. **56**, 384 (1934).
- (3) BAXTER, W. P., AND DICKINSON, R. G.: J. Am. Chem. Soc. **51**, 109 (1929).
- (4) BODENSTEIN, M., AND LIENEWEG, F.: Z. physik. Chem. **119**, 123 (1926).
- (5) BONHOEFFER, K. F., AND REICHARDT, H.: Z. Physik **67**, 780 (1931).

- (6) BOOHER, J. E., AND ROLLEFSON, G. K.: *J. Am. Chem. Soc.* **56**, 2288 (1934).  
(7) BOWEN, E. J., AND CHEUNG, W. M.: *J. Chem. Soc.* **1932**, 1200.  
(8) BOWEN, E. J., MOELWYN-HUGHES, E. S., AND HINSHELWOOD, C. N.: *Proc. Roy. Soc. London* **134A**, 221 (1931).  
(9) CHAPMAN, A. T.: *J. Am. Chem. Soc.* **56**, 818 (1934); **57**, 416 (1935).  
(10) DICKINSON, R. G., AND BAXTER, W. P.: *J. Am. Chem. Soc.* **50**, 774.  
(11) DICKINSON, R. G. AND CARRICO, J. L.: *J. Am. Chem. Soc.* **56**, 1473 (1934).  
(12) DICKINSON, R. G. AND JEFFREYS, C. E. P.: *J. Am. Chem. Soc.* **52**, 4288 (1930).  
(13) DICKINSON, R. G. AND LEERMAKERS, J. A.: *J. Am. Chem. Soc.* **54**, 3852 (1932).  
(14) DICKINSON, R. G. AND NIES, N. P.: *J. Am. Chem. Soc.* In press.  
(15) EGGERT, J., AND BORINSKI, W.: *Z. Physik* **26**, 865 (1925).  
(16) EYBER, G.: *Z. physik. Chem.* **144A**, 1 (1929).  
(17) FARKAS, L.: *Z. physik. Chem.* **23B**, 89 (1933).  
(18) FINKELNBURG, W., SCHUMACHER, H. J., AND STIEGER, G.: *Z. physik. Chem.* **15B**, 127 (1932).  
(19) FRANCK, J., AND RABINOWITSCH, E.: *Trans. Faraday Soc.* **30**, 125 (1934).  
(20) FRANCK, J., SPONER, H., AND TELLER, E.: *Z. physik. Chem.* **18B**, 88 (1932).  
(21) GHOSH, J. C., NARAYANA MURTHI, D. S., AND DAS GUPTA, D. N.: *Z. physik. Chem.* **26B**, 255, 267 (1934).  
(22) HOLMES, H. H., AND DANIELS, F.: *J. Am. Chem. Soc.* **56**, 630 (1934).  
(23) JOST, W.: *Z. physik. Chem.* **134**, 92 (1928).  
(24) JOST, W.: *Z. physik. Chem.*, Bodenstein Festband, p. 291 (1931).  
(25) KASSEL, L. S.: *J. Am. Chem. Soc.* **53**, 2143 (1931).  
(26) LEY, H., AND ARENDS, B.: *Z. physik. Chem.* **15**, 311 (1931).  
(27) LEERMAKERS, J. A., AND DICKINSON, R. G.: *J. Am. Chem. Soc.* **54**, 4648 (1932).  
(28) MOELWYN-HUGHES, E. A.: *Kinetics of Reaction in Solution*. Clarendon Press, Oxford (1933).  
(29) NAGAI, Y., AND GOODEVE, C. F.: *Trans. Faraday Soc.* **27**, 508 (1931).  
(30) NORRISH, R. W. G.: *J. Chem. Soc.* **1929**, 1158.  
(31) OGG, R. A., JR., LEIGHTON, P. A., AND BERGSTROM, F. W.: *J. Am. Chem. Soc.* **55**, 1754 (1933).  
(32) RABINOWITSCH, E.: *Z. physik. Chem.* **19B**, 190 (1932).  
(33) REICHARDT, H.: *Z. Physik* **70**, 516 (1931).  
(34) SCHUMACHER, H. J., AND STIEGER, G.: *Z. physik. Chem.* **12B**, 348 (1931).  
(35) SCHUMACHER, H. J., AND TOWNEND, R. V.: *Z. physik. Chem.* **20B**, 375 (1933).  
(36) SPINKS, J. W. T.: *J. Am. Chem. Soc.* **55**, 428 (1933).  
(37) SPINKS, J. W. T., AND PORTER, J. M.: *J. Am. Chem. Soc.* **56**, 264 (1934).  
(38) STEIN, N. O.: *Trans. Faraday Soc.* **29**, 583 (1933).  
(39) TAYLOR, H. S., AND JUNGERS, J. C.: *J. Chem. Physics* **2**, 452 (1934).  
(40) TURNER, L. A., AND SAMSON, E. W.: *Phys. Rev.* **37**, 1684 (1931).  
(41) UREY, H. C., DAWSEY, L. H., AND RICE, F. O.: *J. Am. Chem. Soc.* **51**, 1371 (1929).  
(42) UREY, H. C., DAWSEY, L. H., AND RICE, F. O.: *J. Am. Chem. Soc.* **51**, 3190 (1929).  
(43) WARBURG, E.: *Ber. preuss. Akad. Wiss. Berlin*, p. 300 (1917).  
(44) WARBURG, E., AND RUMP, W.: *Z. Physik* **47**, 305 (1928).  
(45) WARBURG, E., AND RUMP, W.: *Z. Physik* **58**, 291 (1929).  
(46) WARBURG, O., AND NEGELEIN, E.: *Biochem. Z.* **204**, 497 (1929).

## DISCUSSION

PROFESSOR FRANCK: I am very much impressed by the fact that Dr. Dickinson could study so many interesting photochemical reactions under conditions which allow a comparison between gaseous and liquid states. In regard to the conclusion that in carbon tetrachloride solution a considerable percentage of absorptions by halogens leads to dissociation, I wish to mention that this seems to be in disagreement with general conclusions which Rabenstein and I have presented previously (19). I would expect a very small yield, because a very large back reaction should take place.

The difference between the absorption region which belongs in the gaseous state to a discrete absorption spectrum and the region which is a continuum in the gaseous state is not so important for reactions in the liquid phase. In the gaseous state the absorption in the discontinuum forms an excited molecule with an average life-time of  $\sim 10^{-8}$  seconds or longer. The absorption in the continuum also gives an excited molecule, but with a life-time equal to the time of one oscillation  $\sim 10^{-13}$  seconds. The probability of impacts in the latter case for normal pressure is negligible. But in a liquid the particles are permanently in a state of collision, so that the difference caused by the different life-times vanishes. What remains is only the difference in frequencies; that will mean the smaller or greater surplus of the energy absorbed against the heat of dissociation. In cases in which the yield is of the order of magnitude of 1, we should always expect a reaction (for instance, with the molecules of the solvent) which forms at least one saturated molecule.

DR. OGG: The very low yield for primary photodissociation in solutions which Professor Franck postulates seems difficult to reconcile with data on the iodine-sensitized photodecomposition of ethylene iodide in carbon tetrachloride solution. Here a reaction of the iodine atoms (produced by photodissociation) with the solvent is out of the question. The velocity of the reaction  $I + C_2H_4I_2 \rightarrow C_2H_4I + I_2$  in carbon tetrachloride solution was measured in the case of iodine atoms produced by the known thermal dissociation of iodine molecules. Comparison with the photochemical reaction allows of calculation of the steady state concentration of iodine atoms in the illuminated solutions. From the values for the steady state concentration, it follows that a quantum efficiency for the primary photodissociation of iodine molecules as small as that assumed by Professor Franck would necessitate a rate of recombination of iodine atoms which is improbably small in comparison with known rates of the trimolecular gas phase recombination of halogen atoms.

PROFESSOR FRANCK (communicated): I should like to ask Dr. Ogg if he is content with the statement, "Franck and Ogg agreed in a private

discussion that the case mentioned by Dr. Ogg is a special case which is not contrary to the discussion remarks made by Franck."

DR. OGG (communicated): I regret to state that I cannot agree completely with Professor Franck's statement. In my opinion the ethylene iodide decomposition, far from being a special case, is a very good example for comparison of rates in solution and in gas phase. I do agree, however, that the interpretation of experimental results so far obtained for this reaction is not necessarily in disagreement with the low efficiency postulated by Professor Franck for primary photodissociation in liquid systems. The essential vagueness of the kinetic picture of trimolecular recombination of free atoms in liquids makes a sharp decision regarding this point very difficult. A satisfactory picture of collision processes in solution must be obtained before the point under discussion can be wholly clarified.

## THE CHEMISTRY OF SOME PHOTOREACTIONS IN NON-IDEAL SOLUTIONS

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Modern photochemistry has rather neglected the subject of reactions in solutions, particularly solutions in which the dissolved molecules are markedly affected by the solvent. The latter type is the one I have chosen to call non-ideal solutions, and I wish to discuss those reactions in which the light-sensitive molecule undergoes no net change, i.e., sensitized reactions. The sensitizing molecule may (1) transfer its energy after activation to another molecule by a collision of the second kind, (2) form a complex ion or molecule with one of the reactants, this complex acting as the effective light absorber, or (3) enter into a series of reactions leading to the net reaction for the system with regeneration of the sensitizer. The first of these possibilities has been the most popular in the literature, one of the most general discussions being that of Franck and Levi (2). The paucity of literature concerning the other two types of sensitizing action is probably due in part to the experimental difficulties involved in obtaining exact information concerning the substances involved (such as complex ions or intermediates at low concentrations), and in part to a tendency to accept the collision-of-the-second-kind hypothesis on account of its apparent simplicity. In this paper I wish to discuss some reactions from the standpoint of the classification given above, in order to show what experiments are needed to determine the true mechanisms.

The particular reactions to be considered are some involving the uranyl ion or dyes such as eosin, so that we are dealing with systems in which the primary action of the light is to produce an activated molecule. If we assume that this photoactivated molecule,  $A^*$ , transfers its energy to some other molecule,  $B$ , by a collision of the second kind, thus bringing about a reaction, then we have a competition which may be represented by the equations



This leads to the law  $-d(B)/dt = I_{\text{abs.}} (1/[1 + k_1/k_2(B)])$ , if we assume that any steps occurring after equation 2 are not rate-determining. If

the reaction is a more complex one, this rate law will be mult function of the concentrations. It is to be noted, however, that this law is not specific for processes such as we have included in equations 1 and 2, but may be derived for many other processes, as, for example, any competition between a unimolecular and a bimolecular process. As a rule other complications enter, so that the agreement between this rate law and the experimental results is qualitative rather than quantitative. In order to discuss these complications we must deal with particular reactions.

As our first example let us consider the decomposition of oxalic acid sensitized by uranyl salts. West, Muller, and Jette (7) and also Pierce (5) have attempted to interpret the behavior of this system by assuming that the absorption of light produced activated uranyl ions which transferred their energy to the oxalic acid molecules, causing a decomposition. Such an interpretation encounters several difficulties. First, the absorption of the effective wave lengths by the solution is increased markedly (approaching a definite limit) on the addition of oxalic acid, a fact which is not accounted for quantitatively in this simple theory. Second, the uranium must be considered as present in at least two molecular species, such as the undissociated salt and its ions or two ions containing uranium.<sup>1</sup> This leads to complications in applying the simple law deduced from equations 1 and 2. If we assume that only one molecular species is effective in producing reaction, then the factor  $I_{abs.}$  must be modified so as to represent the light absorbed by that molecule alone. If we assume that all of the activated uranyl compounds are effective, then we must consider that  $k_1$  and  $k_2$  are probably not the same for all the substances, and therefore the experimental results should not fit a simple law such as we have given, but should fit one containing two or more terms, each of which is of that form. It is therefore possible to set up an equation which will take account of the various molecules which contain the sensitizer, but this has not been done by the advocates of this mechanism.

If we adopt the second type of mechanism, the formation of a complex between uranyl ion and some form of oxalate as suggested by Leighton and Forbes (3), the increase in absorption on adding oxalate can be accounted for by assuming that the absorption coefficient is higher for the complex than for the uranyl ion. McGinnis (4) has compared the change in the rate of decomposition of the oxalate over a range of 0.01 to 2 molar hydrogen-ion concentration with the change in absorption over the same range, and concluded that the results could be explained by assuming

<sup>1</sup> This conclusion is based on a consideration of conductance measurements by Dittrich (1), which show that while uranyl salts conduct so well that a considerable amount of ionization must be assumed, the ionization is by no means complete at the concentrations used in photochemical experiments.

that the uranium was present as  $\text{UO}_2^{++}$ ,  $\text{UO}_2\text{HC}_2\text{O}_4^+$ , and  $\text{UO}_2\text{OH}^+$ , but only the light absorbed by the  $\text{UO}_2\text{HC}_2\text{O}_4^+$  was effective in causing decomposition of the oxalate. It follows that the most simple mechanism involves the decomposition of this complex, but the data available do not permit a decision as to whether the final products are obtained immediately or some other intermediates are formed first. One possibility would be that carbon dioxide splits out, leaving a uranyl formate complex which breaks up on the absorption of another quantum of light. Such a process would be useful in accounting for the low quantum yield (approximately 0.6), and might explain the variation in quantum yield with wave length, which was studied in some detail by Leighton and Forbes. Small amounts of formate are actually found in the solution after the reaction has proceeded to a considerable extent, but this cannot be considered very significant unless it is shown that the uranyl formate complex has a photochemical decomposition rate so much higher than the oxalate complex that only small amounts of formate could remain in solution. In order to test these possibilities it is necessary to have measurements of the absorption coefficients and rates of decomposition of uranyl formate solutions for a number of wave lengths of light. This combination of two successive reactions may be considered as a simple example of the third type of mechanism.

Turning to the subject of sensitized photooxidations by dissolved oxygen, we find many more possibilities than for the reaction we have just considered. Even in applying the collision-of-the-second-kind hypothesis we find two different viewpoints expressed in the literature. One advocates a transfer of energy from the activated sensitizer to the oxygen molecule changing it to the  $^1\Sigma$  state, which is assumed to be more reactive than the normal state of the oxygen molecule. The other considers that the energy is transferred to the substance to be oxidized, putting it into a form more susceptible to the action of the oxygen. The latter seems to be the more reasonable assumption, as these oxidations can be brought about by visible light, and there is no reason to believe that any state of the oxygen molecule which can be reached with the aid of such energies is any more reactive than the normal state. A particular example of the application of this theory is found in the recently published work of Schneider (6) on the oxidation of iodide sensitized by uranyl compounds, fluorescein, rhodamine, and quinine bisulfate. His results are in qualitative agreement with the theory, especially in that the long-lived active state of the uranyl compounds is much more effective at low iodide concentrations than the shorter-lived states of the other molecules. This fact alone, however, is not enough to warrant the exclusion of other possible explanations. Schneider's results show many effects which he leaves unexplained, as, for example, the marked influence of acid on the uranyl-sensitized



reaction and the different behavior of lithium and potassium iodides in the same reaction. These are of great importance, as the collision-of-the-second-kind hypothesis requires a simple law as far as the actual reactants are concerned, so these other effects must be explained as due to secondary effects.

The data available at present are not sufficient to establish any of the other possibilities, so we shall just list them briefly, indicating what kind of evidence is needed. The uranyl compounds offer the best opportunity for the application of the "complex" theory, as there is considerable evidence for uranyl compounds being weak electrolytes. If that theory is correct it should be possible to demonstrate that the rate of the reaction is proportional to the amount of complex (or weak electrolyte) present. Such a proof involves a determination of the equilibrium existing in the solution. It is, of course, possible that other factors may influence the rate also in particular reactions, but the most important fact to be fixed for a theory of this kind is the proportionality between the rate and the amount of complex. The amount of complex may be determined by independent methods, such as a study of absorption coefficients, thus giving a check on the conclusions deduced from rates.

The third type of mechanism, the one involving a series of reactions, is extremely adaptable. One possibility which is quite general is that the activated sensitizer forms a peroxide which reacts with the reducing agent. Such a reaction almost certainly enters in the eosin-sensitized oxidations, and this may be a general phenomenon. It is not necessary to show the presence of peroxide in such reactions, unless it can be shown that a detectable amount of peroxide can exist in the solution under the experimental conditions. Another possibility is that the sensitizer may be reduced and then be oxidized by the dissolved oxygen. If the "stationary state" concentration of the reduced form is very low, it would be possible to have this mechanism hold for reducing agents so weak that a blank test in the absence of oxygen would show no reaction. These chemical mechanisms may produce very complicated rate laws, and it may be that the explanation of the failure of the simple collision-of-the-second-kind theory in many reactions is that the actual processes are true chemical reactions rather than merely energy transfers.

In order to arrive at the best solution of these problems the following procedure is suggested:

1. Determination of the formulas and the amounts of the dissolved molecules of the reactants.
2. Determination of the variation of the quantum yield with wave length. This is not a conclusive test but may be of considerable help in that it is known that the transfer of energy is most efficient

when it is the exact amount which can be utilized by the receiving molecule (8). Thus in a reaction involving collisions of the second kind we should expect to find the quantum yield a maximum near the long wave length limit and decreasing toward shorter wave lengths.

3. Determination, quantitatively, of the effect of altering the concentration of each substance present in the solution, including hydrogen ion.

With complete information available all the possible theories could be tested, and it would not be surprising if we found examples of all three types.

#### REFERENCES

- (1) DITTRICH: *Z. physik. Chem.* **29**, 469 (1899).
- (2) FRANCK AND LEVI: *Z. physik. Chem.* **27B**, 409 (1935).
- (3) LEIGHTON AND FORBES: *J. Am. Chem. Soc.* **51**, 3139 (1930).
- (4) MCGINNIS: Thesis, University of California, 1935.
- (5) PIERCE: *J. Am. Chem. Soc.* **51**, 2731 (1929).
- (6) SCHNEIDER: *Z. physik. Chem.* **28B**, 311 (1935).
- (7) WEST, MULLER, AND JETTE: *Proc. Roy. Soc. London* **121A**, 294 (1928).
- (8) ZEMANSKY: *Phys. Rev.* **36**, 919 (1930).

#### DISCUSSION

DR. W. G. LEIGHTON (Pomona College): Professor Rollefson has suggested the possibility that the quantum yield in the uranyl oxalate photolysis ( $\Phi = \text{ca. } 0.6$ ) is less than unity because of absorption by uranyl formate, itself produced in the reaction. If such absorption is a significant factor, both a decrease in quantum yield and an increase in absorption should be observed through the early stages of photolysis, as the formate begins to accumulate. Bearing on this it is recalled that, in a series of some fourteen determinations of quantum yield at  $\lambda$  366 m $\mu$  reported with Forbes, we found no systematic change in either the yield or the absorption coefficient over the range 2 per cent to 16 per cent oxalic acid decomposed. These results were obtained with a solution containing initially five moles of oxalic acid to one of uranyl sulfate.

The low quantum yield in uranyl oxalate might be accounted for through recombination of photochemical products, or again, through deactivation of excited uranyl oxalate complex by water molecules. Similarly, the inhibitory effect of  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{SCN}^-$ , and  $\text{I}^-$  could possibly be interpreted as due to deactivation of the excited complex by these ions, although the complex-forming tendencies of these ions should not be overlooked.

In support of the "complex" theory as applied to the uranyl oxalate photolysis, it seems appropriate to present certain data which we have

used in attempting to apportion the energy absorbed in this system. The curve in figure 1, like one described by Ghosh and Mitra, shows the striking increment in absorption coefficient when oxalic acid is added to a fixed concentration of uranyl sulfate. As plotted, none of the increase is due to absorption by the oxalic acid itself, as correction was made for this contribution (nearly negligible at  $\lambda$  313  $m\mu$ ). The curve is just what would be expected if a strongly absorbing complex is formed, or perhaps an equilibrium mixture of such compounds. If a single complex predominates under the experimental conditions, its absorption coefficient should correspond approximately to the limit approached by the curve. Along the

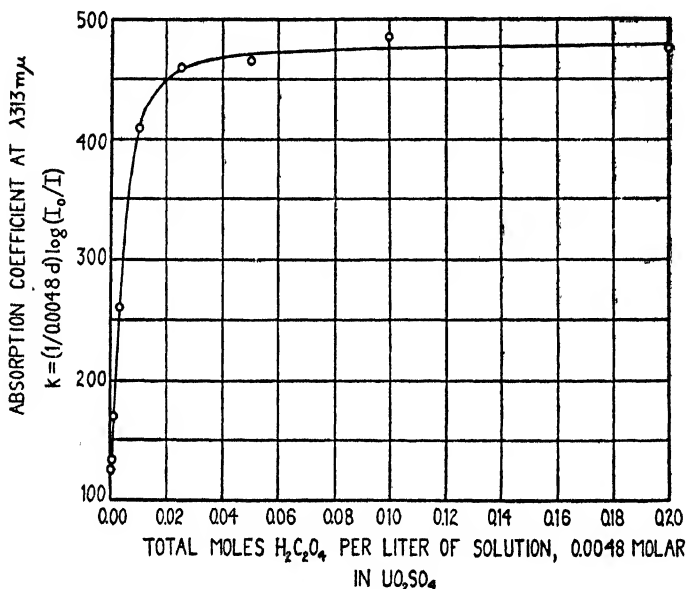


FIG. 1

steep part of the curve the equilibrium concentrations could then be calculated, as was done by Ghosh and Mitra, from the equation

$$\log \left( \frac{I_0}{I} \right)_{\text{observed}} = \sum kc = k_{\text{UO}_2\text{SO}_4} \cdot ([\text{UO}_2\text{SO}_4, \text{total}] - [\text{complex}]) + k_{\text{complex}} \cdot [\text{com}]$$

Equilibrium concentrations calculated from the experimental curve by means of this equation are shown in table 1. In the last column the stability constant of the complex is calculated, assuming that the predominating complex contains one oxalate and one uranyl group. The constancy obtained is perhaps as good as could be expected, considering the fact that

both the effect of hydrogen ion on the equilibrium and also the possible presence of a higher complex were disregarded. A similar calculation assuming the predominating complex to contain two oxalates with one uranyl group gave values for the stability constant ranging from  $K = 5 \times 10^4$  in a 1:5 mixture to  $K = 70 \times 10^4$  in a 1:2 mixture, becoming infinite at somewhat lower excess of oxalic acid. Apparently the former

TABLE 1

*Equilibrium concentrations and stability constant of the uranyl oxalate complex*

TOTAL MOLES PER LITER		$k_{\text{cobd.}}^*$	EQUILIBRIUM CONCENTRATIONS			STABILITY CONSTANT
$\text{UO}_2\text{SO}_4$ $u$	$\text{H}_2\text{C}_2\text{O}_4$ $a$		$\text{UO}_2\text{SO}_4$ $u - X$	$\text{H}_2\text{C}_2\text{O}_4$ $a - X$	" $\text{UO}_2\text{C}_2\text{O}_4$ " $X$	$X$ $(u - X)(a - X)$
0.0048	0 1-0.2	2 31±	0.0000	0.1-0 2	0.0048	
0 0048	0 0000	0.60	0 0048	0 0000	0.0000	
0.0048	0.0250	2 20	0 0003	0 0205	0.0045	$7 \times 10^2$
0.0048	0.0100	1.96	0 0010	0 0062	0 0038	$6 \times 10^2$
0 0048	0 0030	1.25	0 0030	0 0012	0.0018	$5 \times 10^2$
0.0048	0 0010	0.81	0.0042	0 0004	0 0006	$4 \times 10^2$

\*  $\lambda 313 \text{ m}\mu$  (corrected for absorption by excess oxalic acid).

TABLE 2

*Quantum yield referred to the uranyl oxalate complex*

MOLES PER LITER			RELATIVE ABSORPTION BY COMPLEX† AT $\lambda 313 \text{ m}\mu$	QUANTUM YIELD AT $\lambda 313 \text{ m}\mu$	
Total		Equilibrium*		Gross	Referred to complex
$\text{UO}_2\text{SO}_4$ $u$	$\text{H}_2\text{C}_2\text{O}_4$ $a$	" $\text{UO}_2\text{C}_2\text{O}_4$ " $X$	$\frac{k_x X}{\Sigma k c}$	$\Phi_g$	$\Phi_g \frac{\Sigma k c}{k_x X}$
0 001	0 050	0.0009(7)	0 98	0.57(7)	0.59
0 010	0.050	0.0096	0 99	0.56(1)	0 57
0 020	0.040	0.0186	0 98	0 55(5)	0 57
0.010	0.010	0.0067	0.89	0 51(5)	0 58

\*  $X$  follows from the stability constant,  $K = 6 \times 10^2$  (table 1).

†  $k_u = 125$ ,  $k_x = 480$ ,  $k_a = 0.2$ ;  $\Sigma k c = k_u(u - X) + k_x X + k_a(a - X)$ .

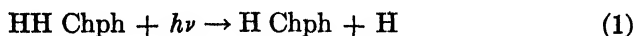
assumption, as illustrated in table 1, is more nearly correct in the case of the mixtures studied. To be sure this conclusion does not distinguish between such possibilities as  $\text{UO}_2\text{C}_2\text{O}_4$  and  $\text{UO}_2\text{HC}_2\text{O}_4^+$ , etc. This question now seems to be answered in favor of  $\text{UO}_2\text{HC}_2\text{O}_4^+$ , according to Professor Rollefson.

In table 2 the equilibrium concentration and relative absorption of the

of attacking the problem was presented by Kautsky (7), who studied the fluorescence of living leaves under different conditions and especially the influence of oxygen on the light emission. Since reëmitted light can not be used for photochemical processes, researches on fluorescence and its quenching allow conclusions to be drawn about the photochemical yield. Kautsky found that the intensity of fluorescence was not constant but was a complicated function of the time of irradiation, and he explained his results with assumptions which seem not to be in accordance with other experience in the field of fluorescence of liquids. The author therefore made an attempt to discuss the photochemical part of photosynthesis in a way which avoids these difficulties and offers possible explanations for the features of photosynthesis mentioned above.

For the sake of simplicity we will use in the following equations the symbols: HH Chph for fully hydrogenated chlorophyll; H Chph for monodehydrochlorophyll; Chph for dehydrogenated chlorophyll; OH Chph for dehydrogenated chlorophyll to which is bound one OH radical.

The binding force of one H atom in HH Chph can be calculated (4) from the color of the afterglow of irradiated chlorophyll observed by Kautsky in chlorophyll solutions in the absence of oxygen, if one assumes that the afterglow is excited by the recombination process between H and H Chph. This value allows one then to calculate a lower limit for the binding force of the second loosely bound H atom from the stability of HH Chph, which does not disintegrate spontaneously into  $H_2$  and Chph. An upper limit can be derived by the assumption that HOH Chph is unstable and will break up into  $H_2O$  and Chph. This instability of HOH Chph would make it impossible that HH Chph can be used for the process of photosynthesis. Before photosynthesis starts a so-called induction period takes place. It is assumed that in this time H Chph is formed. This process is described by the following equations:



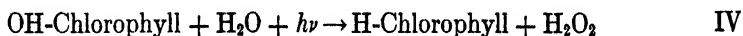
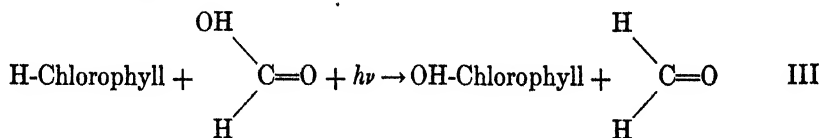
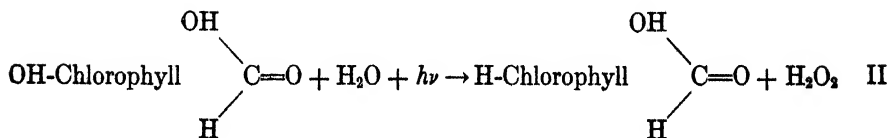
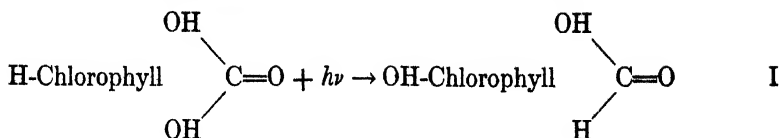
The yield of equation 1 is very low, because (5) two radicals formed in solution recombine to a large extent. If oxygen is not present, a somewhat slower back reaction will practically entirely restore HH Chph and give an afterglow by chemiluminescence. If oxygen is present, reaction 1 is followed by:



Equation 1 having a low quantum yield, the process of converting HH Chph to H Chph in the presence of oxygen takes a time from several

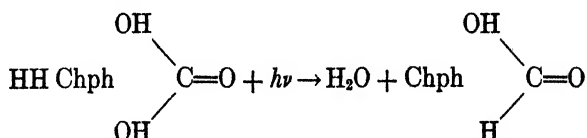
seconds to a minute, being of course a function of the intensity of the irradiating light.

The main processes are given by the following equations:



The process induced by the light is in all these four equations an exchange between an H atom and an OH radical. The binding energies of H and OH in carbon dioxide and in formic acid are practically the same, as can be shown by thermochemical results. Also if we assume for OH Chph a very weak binding force, reaction I should be slightly exothermic. Under the same assumption about OH Chph, reactions II and IV should easily proceed in the same direction as the arrow.

If radiation is stopped the H Chph can take up a second hydrogen atom in the dark, in a slow reaction with formic acid or formaldehyde, destroying a small part of the substances gained by photosynthesis. This interprets Kautsky's results, which indicate that the same intensity-time relationship after exposure to light is reproducible only after a lapse of the order of fifteen minutes in the dark. In the absence of oxygen the reaction which takes place should be



followed by a slow back reaction in the reverse direction. Dehydrogenated chlorophyll will thus reëmit light, not being able to start one of the photochemical reactions mentioned above. The shape and intensity of Kaut-

sky's intensity-time curves can be interpreted on the basis of the assumptions made above. Those assumptions are suggested as working hypotheses. It is of course possible to use the four main equations but replace in them H Chph by HH Chph and OH Chph by HOH Chph. But this would have sense only if one abandons the hypothesis that HOH Chph is unstable.

The main points of the interpretation given above are as follows:

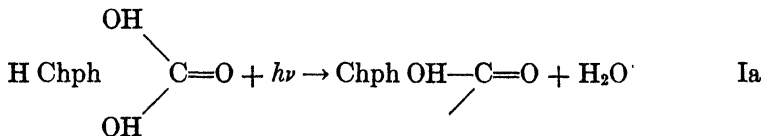
1. If four quanta are necessary to reduce one carbon dioxide molecule, four different photochemical reactions have to be considered, since assumptions about storing up energy in the form of excitation energy of molecules are impossible. Also hypotheses about metastable states with a long life-time cannot be assumed because the reactions take place in a condensed system.

2. Each photochemical partial reaction has to correspond to the energy amount of one quantum of red light, which gives photosynthesis.

3. Each individual photochemical step has to take place with the yield 1, in accordance with the total quantum yield. Therefore, only those photochemical partial reactions may be considered in which at least one of the products is not a radical, so that back reactions would not take place.

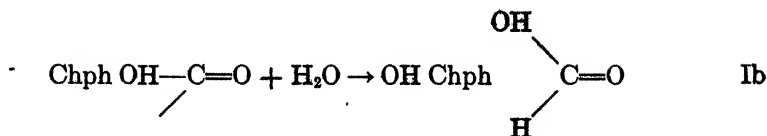
#### REMARKS ADDED AFTER THE DISCUSSION

A difficulty in the system of reactions presented above is the assumption in equations I and III that an exchange of places between an H atom at the H Chph and an OH radical at the carbon dioxide shall take place in one elementary act.<sup>1</sup> It is possible to avoid this difficulty in assuming two steps for these reactions. If the binding force between H and Chph is not larger than  $\sim 64$  kg-cal. (which may be plausible for loosely bound hydrogen compared with the normal C—H binding force  $\sim 90$  kg-cal.), this can be done. It will be enough to discuss only equations Ia and Ib. The replacement of equation III by two steps has to take place in a corresponding way.



followed by a dark reaction

<sup>1</sup> See, for instance, the discussion remark of Bates, but I may use the opportunity to mention also letters received from F. O. Rice of Baltimore and Schoenberg of Edinburgh, which point out the same difficulty.



The condition that equation Ia can take place with the yield 1 is that the quanta are not big enough to split off the hydrogen atom from the chlorophyll. Quanta of ultra-violet light which could do so should then give a much smaller quantum yield if they are absorbed at all by the chlorophyll. The dissociation process should be followed in most cases by a back reaction instead of the water formation. For equation Ib, one should expect a heat of activation so that the reaction velocity is dependent on the temperature. Reaction Ib seems to fulfill all the conditions which are necessary to understand the results published in very interesting papers by Emerson and Arnold (2) and Arnold and Kohn (1). Also Kautsky's intensity-time relations may be interpreted in this way, but more experimental proof is necessary here.

The exchange of places between H and OH according to equations II and IV will not offer such difficulties, as is pointed out by Pauling in the discussion (see below).

The assumption that H Chph and not HH Chph plays the important rôle for photosynthesis was founded on Willstätter and Stoll's results that oxygen is necessary to start photosynthesis, and on Kautsky's observation concerning the afterglow of the fluorescence. Gaffron (6) has published in the meantime a paper in which he states that photosynthesis starts also without oxygen. He explains Willstätter and Stoll's results by the presence of products of fermentation, which poison photosynthesis and have to be removed, for instance, by longer irradiation. This result is not contrary to the assumptions put forward above. It is reasonable to assume other acceptors for hydrogen atoms in the plant if oxygen is not present. Also carbon dioxide may act as acceptor, but the other acceptors will of course not be so effective as oxygen. The result of a lack of oxygen would then be that the induction period is lengthened. But we have also to consider the possibility that the hypothesis is wrong and that HH Chph is the important substance in photosynthesis. As was mentioned above, the four main equations can then be used in the same way, substituting always HH Chph for H Chph and HOH Chph for OH Chph. In this case it would be necessary to assume that the first hydrogen atom is bound more strongly to the H Chph than was calculated from the afterglow ( $\sim 64$  kg-cal. instead of  $\sim 40$  kg-cal.). The basis for this calculation was that the afterglow also occurs with red light. Kautsky supposes so, but his observations are made with the whole light of an arc, so that this point



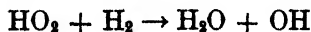
needs more experimental evidence. It may be also that HH Chph and H Chph are equally important, the first for photosynthesis with longer wave lengths, the second for shorter wave lengths. Kautsky's observations on the fluorescence in living leaves are made with blue light and even shorter wave lengths.

#### REFERENCES

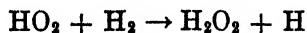
- (1) ARNOLD, W., AND KOHN: J. Gen. Physiol. **18**, 109 (1934).
- (2) EMERSON, R., AND ARNOLD, W.: J. Gen. Physiol. **15**, 391 (1932); **16**, 191 (1932).
- (3) FISHER, H.: J. Chem. Soc. **1934**, 246.
- (4) FRANCK, J., AND LEVY: Naturwissenschaften **23**, 226 (1935).
- (5) FRANCK AND RABINOWITSCH: Trans. Faraday Soc. **30**, 152 (1934).
- (6) GAFFRON, H.: Naturwissenschaften **23**, 528 (1935).
- (7) KAUTSKY, H., HIRSCH, H., AND DAVIDSHÖFFER, F.: Ber. **65**, 1762 (1932).
- (8) STOLL: Naturwissenschaften **20**, 955 (1932).
- (9) WARBURG, O.: Biochem. Z. **103**, 188 (1920).
- (10) WILLSTÄTTER, R.: Naturwissenschaften **21**, 252 (1933).
- (11) WILLSTÄTTER AND STOLL: Chlorophyllbuch. Bayr. Akad.

#### DISCUSSION

PROFESSOR BATES: Professor Franck, in discussing the energetics of the various steps in his mechanism, mentioned only the change in heat content. Is it not possible that there might be large activation energies involved which would change the whole complexion of things? For example, step 4 is of the type that in the gas phase usually requires considerable activation energy, being a "double displacement." In the mechanism for the hydrogen atom-oxygen reaction we find evidence that the reaction corresponding to 4,



requires enough activation energy to make the reaction occur either through



or



PROFESSOR LINUS PAULING (California Institute of Technology): Professor Franck has postulated that in the active state much of the chlorophyll is present in the form of H Chph or OH Chph. Each of these molecules contains an odd number of electrons, and has a magnetic moment of 1.73 Bohr magnetons. Hence their presence could be detected by measurements of the magnetic susceptibility of the illuminated substance.

Dr. Bates has remarked that the activation energies for the reactions postulated by Professor Franck may be very large. It may be that this is avoided because of the special properties of the odd molecules; for example, a water molecule may be attached by the free valence of OH Chph in such a way that the hydrogen peroxide-producing reaction follows immediately the formation of a single bond between the two oxygen atoms, for which the activation energy may be small.

PROFESSOR FRANCK: I agree entirely with the remarks of Dr. Pauling, but for the main equations 1 and 3, difficulties similar to those mentioned by Dr. Bates remain (see the improvement made in the last section of the paper "Remarks on Photosynthesis").

DR. LARS ONSAGER (Yale University): According to the scheme suggested by Dr. Franck, it appears that hydrogen peroxide in sufficient concentration ought to react with H-chlorophyll with the emission of light. Has this reaction been investigated? Might I also ask if Dr. Franck considers it possible to carry on photosynthesis *in vitro*?

PROFESSOR FRANCK: So far as I am aware, research regarding chemiluminescence in this special case has not been carried out. It would be difficult to separate this light emission from other processes which give light, for instance, fluorescence. Moreover, I would expect if at all a very weak effect, because the reaction should be endothermic and the concentration of H Chph is very small. Photosynthesis *in vitro* has never succeeded up to this time. Still I hope that it would be possible to find the right conditions. The difficulty seems to be that Chph in water gives, not a real solution, but a colloid in which one Chph molecule which absorbs light attacks another one. It would be necessary to imitate the chloroplasts. That will mean that it would be necessary to have Chph molecules scattered on the surface of a stable lipid colloidal substance in water.

DR. JAMES H. C. SMITH (Carnegie Institution of Washington, Stanford): The interpretation which Professor Franck has given to the experimental observations of Kautsky on the fluorescent effects in leaves (Kautsky, Hans, Hirsch, A., and Flesch, W.: Ber. **68**, 152 (1935) and on the afterglow of chlorophyll in solution (Kautsky, Hans, Hirsch, A., and Davidshöffer, F.: Ber. **65**, 1762 (1932)) is very interesting. The chief significance of this proposal lies in its reasonable correlation of some of the photochemical phenomena occurring in photosynthetic organs with observations made on simpler photochemical systems. These correlations will undoubtedly aid in the interpretation of the photosynthetic process.

The quenching of the fluorescence and afterglow of chlorophyll by oxygen has been interpreted by Professor Franck to be a reaction between oxygen and the hydrogen dissociated from chlorophyll by the action of

light, which reaction forms monodehydrochlorophyll. This reaction is assumed to be necessary to prepare the chlorophyll for the subsequent reduction of carbon dioxide. In this scheme oxygen is necessary for the initiation of the photosynthetic reactions. Recent experiments by Gaffron (*Naturwissenschaften* **23**, 528 (1935)) have indicated that molecular oxygen is not necessary for carbon assimilation, and on the basis of these experiments it appears probable that molecular oxygen is not involved in the first step in photosynthesis.

Gaffron has also shown that immediately following illumination carbon dioxide was absorbed more quickly than oxygen was evolved. This is significant in that it indicates that carbon dioxide absorption and oxygen evolution may be distinct processes. This agrees with Professor Franck's proposed reactions, in that the evolution of oxygen from the hydrogen peroxide formed by the reduction of carbon dioxide would be a step separate from the absorption of the carbon dioxide.

In a discussion such as this, one should probably limit oneself to the details of the paper presented, but in this instance it seems advisable to point out that photosynthesis is a complicated biological process in which many factors are operative, the disentanglement of which and the evaluation of their individual contributions will require considerable experimentation.

While it is desirable to reduce the photosynthetic process to simple terms, experiments on plants indicate that the process is very complex. Harder's experiments (*Planta* **20**, 699 (1933)) have shown that the effects caused by light of different intensities are complicated. The plant's behavior is conditioned by its previous history. The rate of photosynthesis is a function of the ratio of the light used in cultivation and in measurement. When the ratio of intensity of light of cultivation to intensity of light used in measurement is small, there is a rapid acceleration in the rate of photosynthetic activity with time. When the ratio is large there is a rapid decrease in the photosynthetic rate. These effects persist for a considerable period of time. Other factors, such as length of periods of illumination, nutrition, and temperature, cause complicated effects. In view of these observations it scarcely seems probable that the photosynthetic reactions can be circumscribed by as simplified a process as has been proposed by Professor Franck.

One other relation should also be mentioned in connection with the proposed mechanism. In all photosynthetic organisms which have been investigated thus far, whether the purple bacteria or the higher plants, the *green* pigments are always accompanied by the *yellow* pigments. The individual pigments in the purple bacteria differ from those in the higher plants, but the same type of complex apparently exists (van Niel, C. B.,

and Smith, James H. C.: Arch. Microbiologie 6, 219 (1935)). Although it is dangerous to conclude that because the *yellow* pigments always accompany the *green* pigments in the photosynthetic organs they must be involved in the photosynthetic reactions, it seems highly probable, because of this close association, that they may play a rôle in the process and ultimately may have to be included in the formulation of the reactions involved.

PROFESSOR FRANCK: I had not seen Gaffron's paper until now, but so far as I understand these results, they are not in contradiction to my assumptions because oxygen can be replaced by other less effective acceptors of hydrogen atoms in the plant (see the remarks added to the paper).

With the general remarks of Dr. Smith I agree, in so far as I do not claim to have the real solution of the whole problem. I wish only to show that it is possible to sketch a picture with a few simple assumptions. The only point which is in favor of my picture seems to be that I use only principles which are in accordance with the results of atomic physics.

As to the last remarks, I may mention that most of the experiments made with plants and also the interesting experiments with flashlights (Emerson and Arnold) are carried out under conditions in which an over-dosage of light is used. This gives, of course, very interesting and important results, but of course not very simple ones, which only can be expected if the amount of light, the amount of Chph and  $\text{CO}_2$ , etc., are carefully balanced against each other, as was done in Warburg's experiments with the quantum yield (see the remark added to the paper).

DRS. O. L. INMAN AND PAUL ROTHMUND (Kettering Foundation, Antioch College) (communicated): We are yet unwilling to accept Dr. Franck's statement that "it is known that in the process of photosynthesis four light quanta which are absorbed from chlorophyll and transferred to the carbon dioxide are used to reduce one carbon dioxide molecule to formaldehyde and to make one oxygen molecule free." It seems to us necessary that Warburg's work should be carefully substantiated before we accept these as established facts in the photosynthetic mechanism. The statement that oxygen is necessary to initiate photosynthesis is not by any means a settled question. E. N. Harvey (Plant Physiol. 3, 85 (1928)) concluded that several marine algae and one flowering plant (*Zostera*) could carry out the first steps of photosynthesis in the absence of oxygen even to a pressure which corresponds to about  $10^{-53}$  atmospheres. Harvey's work has been successfully repeated by us with a large variety of land plants. Such hypotheses as Dr. Franck's have value, since they tend to focus attention on certain phases of the supposed mechanism which need more experimental support.

DR. VERNON M. ALBERS (Kettering Foundation, Antioch College)

(communicated): Dr. Knorr and I have studied the fluorescence spectra of the chlorophylls and some of their derivatives, during photodecomposition, in acetone solution, under atmospheres of air, oxygen, carbon dioxide, and nitrogen, using the total radiation from Pyrex mercury arcs. The time required to bleach a solution of a given substance varied with the different atmospheres, in general being greatest under oxygen and least under nitrogen, but the intensity of the fluorescence was not noticeably different. In some cases the rate of bleaching was as much as twenty times as great under nitrogen as under oxygen. This would indicate that in these solutions of the chlorophylls and chlorophyll derivatives the yield of fluorescence is not inversely proportional to the photochemical yield, but is independent of the photochemical yield.





